VOLUME XVIII

Number 11

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DISEASES *of the* NERVOUS SYSTEM

A Practical Journal on Psychiatry and Neurology

NOVEMBER

1957

(CONTENTS ON PAGE 408)

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References:
1. Sainz, A.: Personal communication.
2. Hutchinson, J. T.: Evaluation of Pacatal in Psychotic States, address before the American Psychiatric Association, Nov. 16, 1956.
3. Bowes, H. A.: Am. J. Psychiat. *113*:530 (Dec.) 1956.

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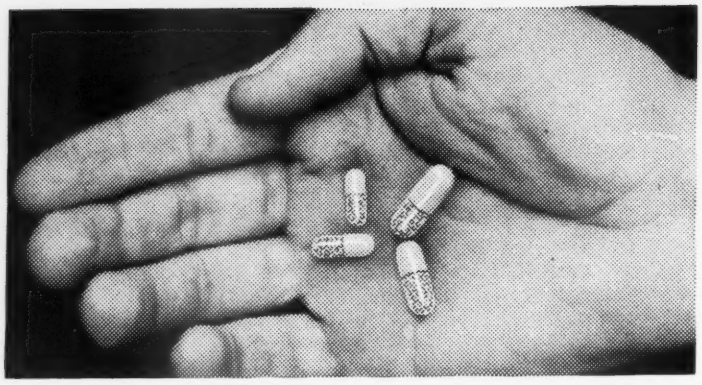

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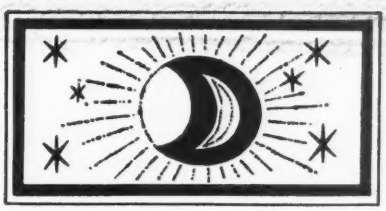

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Volume XVIII NOVEMBER 1957 Number 11

DISEASES *of the* Nervous System

Contents

PERIPHERAL NEUROPATHY ASSOCIATED WITH MULTIPLE MYELOMATOSIS AND AMYLOIDOSIS 419
Lawrence W. Dumas, E. H. Rentschler and Kenneth M. Earle

REACTIVITY OF BRAIN TISSUE TO INTRACRANIAL AND EXTERNAL ELECTROTHERAPY 425
Juan Negrin, Jr.

PROCHLORPERAZINE (COMPAZINE) IN EMOTIONAL DISTURBANCES 430
Louis G. McAfoos, Jr.

DIMETHYLANE IN THE TREATMENT OF ANXIETY REACTIONS 434
Jmaes M. A. Weiss, Thomas T. Flynn and Robert M. Counts

ELECTROSHOCK THERAPY WITHOUT MUSCLE RELAXANTS 439
J. M. Radzinski

PRELIMINARY REPORT ON CYTOPATHOLOGY OF ERYTHROCYTES OF SCHIZOPHRENIC PATIENTS 444
H. R. Ansley, W. H. Sheldon, A. M. Tenney and R. D. Elderkin

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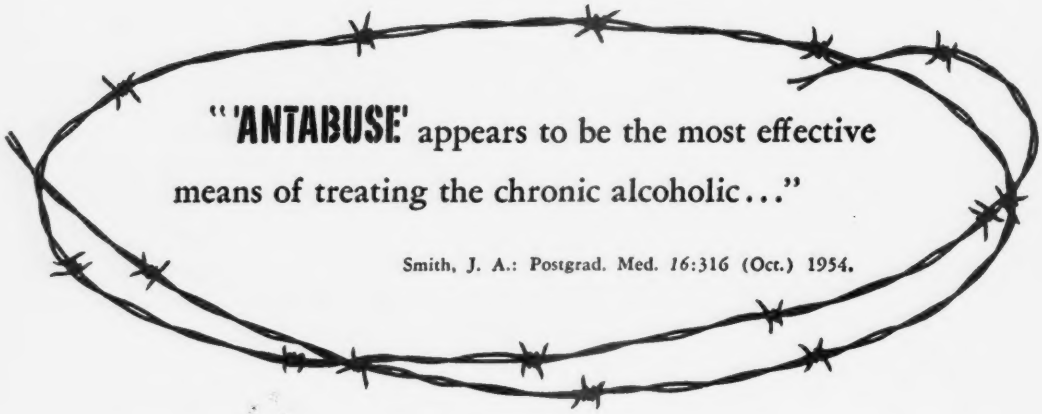

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references: (1) Settel, E.: Am. Pract. & Digest Treat. *8*:443, 1957.
(2) Batterman, R. C., and Grossman, A. J.: Federation Proc. *14*:316, 1955.

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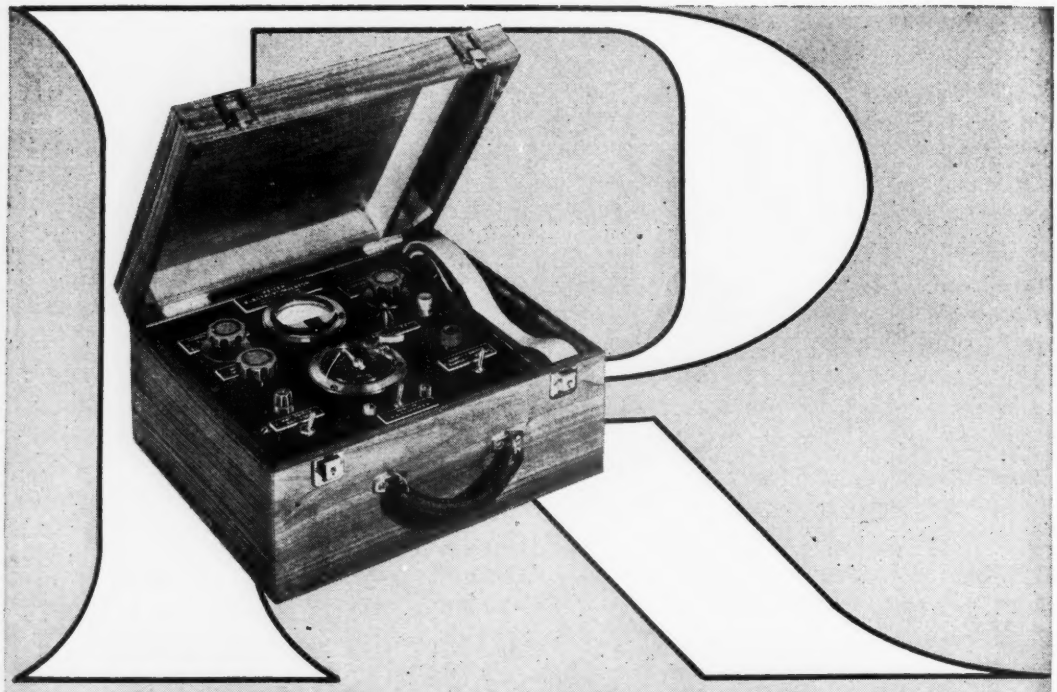

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pharmacologically improved

Enhanced potency with far less sedative effect

clinically improved

Does not oversedate the patient into sleepiness, apathy, lethargy

Drug-induced agitation minimal

Active and rapid in controlling manic states, excitement and panic... in modifying the disturbing effects of delusions and hallucinations... in moderating hostile behavior...in facilitating insight

Intractable behavior patterns brought under control... patients made accessible to psychotherapy...nursing care reduced... social rehabilitation hastened

Effective dosage levels may be reached without development of side effects

VESPR

WHAT IS IT? Vesprin—Squibb Triflupromazine—is a new, improved agent for better management of psychotic patients. It is useful in schizophrenia, manic states and psychoses associated with organic brain disease.

Vesprin is chemically and pharmacologically improved. The phenothiazine structure has been modified, resulting in potentiation of beneficial properties and in reduction of unwanted effects. Pharmacologically, Vesprin shows an enhanced potency with far less sedative effect.

CLINICAL EXPERIENCE: Data in over 600 of the hundreds of patients treated with Vesprin to date have been carefully analyzed.

In 1 series of 55 hospitalized psychotic patients treated with Vesprin, marked to moderate improvement occurred in approximately 66 per cent.

Five patients were discharged from the hospital. Two of these patients had not responded to any previous treatment.

In another small series of patients, which included 12 disturbed children, some improvement was seen in 11 of the 12 children who were treated with Vesprin for at least 2 months. In none of the children were any significant side effects observed.

In a third series of 123 psychotic patients treated with Vesprin for more than 3 months, 5 recovered from all of their active psychotic manifestations, particularly delusions and hallucinations, and 24 recovered from most psychotic manifestations with good social remission. An additional 78 patients showed significant improvement in their psychotic behavior.

Another group of schizophrenic patients has been treated with Vesprin for periods ranging from 6 months to 1 year. During this time clinical laboratory studies were made weekly, and later monthly, on urine and blood of the patients.

Although leukocyte counts showed some tendency to decrease, there were no abnormally low counts. Though hemoglobin levels tended to show some increase, it was not significant. Liver function tests performed during the final 2 months of treatment were entirely negative.

This investigator concluded that these laboratory

a new,
improved agent
for better
management
of
psychotic
patients

IN

Squibb Triflupromazine

In extensive clinical experience—singularly free from toxicity

- **Jaundice or liver damage...not observed**
- **Skin eruptions...rare**
- **Photosensitivity...rare**
- **Blood dyscrasias...not observed**
- **Hyperthermia...rare**
- **Convulsions...not observed**

studies gave no evidence of drug toxicity.
Another investigator thought that Vesprin appeared to be more active and rapid in effect. The best response to Vesprin was seen in overactive, troublesome schizophrenic patients.

WHAT ARE THE ADVANTAGES? Clinical experience in hundreds of patients has shown that Vesprin does not oversedate the patient into sleepiness, drowsiness and lethargy. Drug-induced agitation is minimal.
Vesprin is active and rapid in controlling manic states, excitement and panic, and also in controlling the disturbing effects of delusions and hallucinations. Vesprin moderates hostile behavior and facilitates insight.
With Vesprin, intractable behavior patterns are rapidly brought under control. Thus, patients are made accessible to psychotherapy. Nursing care is reduced, and the patients' social rehabilitation is facilitated.
Extensive clinical experience has shown Vesprin to be singularly free from toxicity. Clinicians who have worked with the drug over long periods have not seen jaundice or liver damage, blood dyscrasias, or convulsions. Skin eruptions, photosensitivity or hyperthermia have been rarely observed.

WHAT ARE THE SIDE EFFECTS? Investigators have reported such symptoms as dizziness, nausea, weakness, drowsiness and epigastric distress in patients treated with Vesprin. Postural hypotension has been seen occasionally in normotensive patients. A hypotensive effect has been observed in patients with high blood pressure.
Anxiety and restlessness have been observed in some patients, and gain in weight in a few. These effects have usually been mild, and, as a rule have disappeared when the dosage was reduced or treatment stopped.
The most commonly encountered side effect has been the development of a Parkinson-like syndrome with motor disturbances and extrapyramidal symptoms. This syndrome is reversible and symptoms usually subside with a reduction of dosage or discontinuance of medication for 2 or 3 days.

VESPRIN

Squibb Trifluprom azine

WHEN IS IT INDICATED? Vesprin is indicated in treatment of various acute and chronic psychoses. Because it ameliorates psychomotor hyperactivity and assaultive behavior, Vesprin is particularly useful in management of schizophrenia, manic states, sociopathic personality disturbances with psychotic reactions, mental deficiency with psychoses, and psychoses associated with organic brain disease and senility.
Contraindications: Vesprin is contraindicated in comatose states due to central nervous system depressants (alcohol, barbiturates, opiates).

WHAT IS THE DOSAGE? The recommended adult dosage of Vesprin is 25 mg. t.i.d., to be adjusted according to patient response. This dose may be increased until the desired clinical effect has been achieved, or until unwanted side effects become a problem.
The initial dose for children is 10 mg. t.i.d.
The suggested starting dose in geriatric patients is 10 mg. t.i.d. The dosage in children and elderly patients may be increased according to patient response.

The optimum dose of Vesprin varies from patient to patient and should be established on an individual basis. In the majority of patients, prolonged treatment is required for maximum clinical response.
Caution: Although no deleterious effects on the hemopoietic system have occurred to date in the extensive clinical use of Vesprin, routine blood counts are suggested during the course of therapy.
Patients should be watched for indications of soreness of the mouth, gums or throat, or for symptoms of upper respiratory infection. If these complications occur, and a confirmatory leukocyte count indicates cellular depression, the agent should be stopped and appropriate treatment, including intensive antibiotic therapy, should be started immediately.

HOW IS IT SUPPLIED? Vesprin is supplied in tablets of 10 mg., 25 mg., and 50 mg. in bottles of *50 and 500.*

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for example:

in multiple sclerosis Seven of 10 patients showed objective improvement, with "...undoubted reduction in spasticity..." in two days to four weeks.[1]

In another series—"All of the five patients with multiple sclerosis showed measurable diminution of painful spasticity..."[2]

in cerebral palsy "The administration of zoxazolamine (Flexin) in 28 children, each of whom had spasticity, produced a decrease of muscular tone on passive flexion in every instance."[3]

"Of ten patients who received zoxazolamine (FLEXIN) for a one-month period, small but significant improvements in tests of motor function were observed in six patients and some degree of improvement was apparent in one."[4]

references (1) Rodriguez-Gomez, M.; Valdes-Rodriguez, A., and Drew, A. L.: J.A.M.A. 160:752 (Mar. 3) 1956. (2) Settel, E.: Am. Pract. & Digest Treat. 8:443 (March) 1957. (3) Abrahamsen, E. H., and Baird, H. W., III: J.A.M.A. 160:749 (Mar. 3) 1956. (4) Millichap, J. G., and Hadro, R.: Neurology 6:843 (December) 1956.

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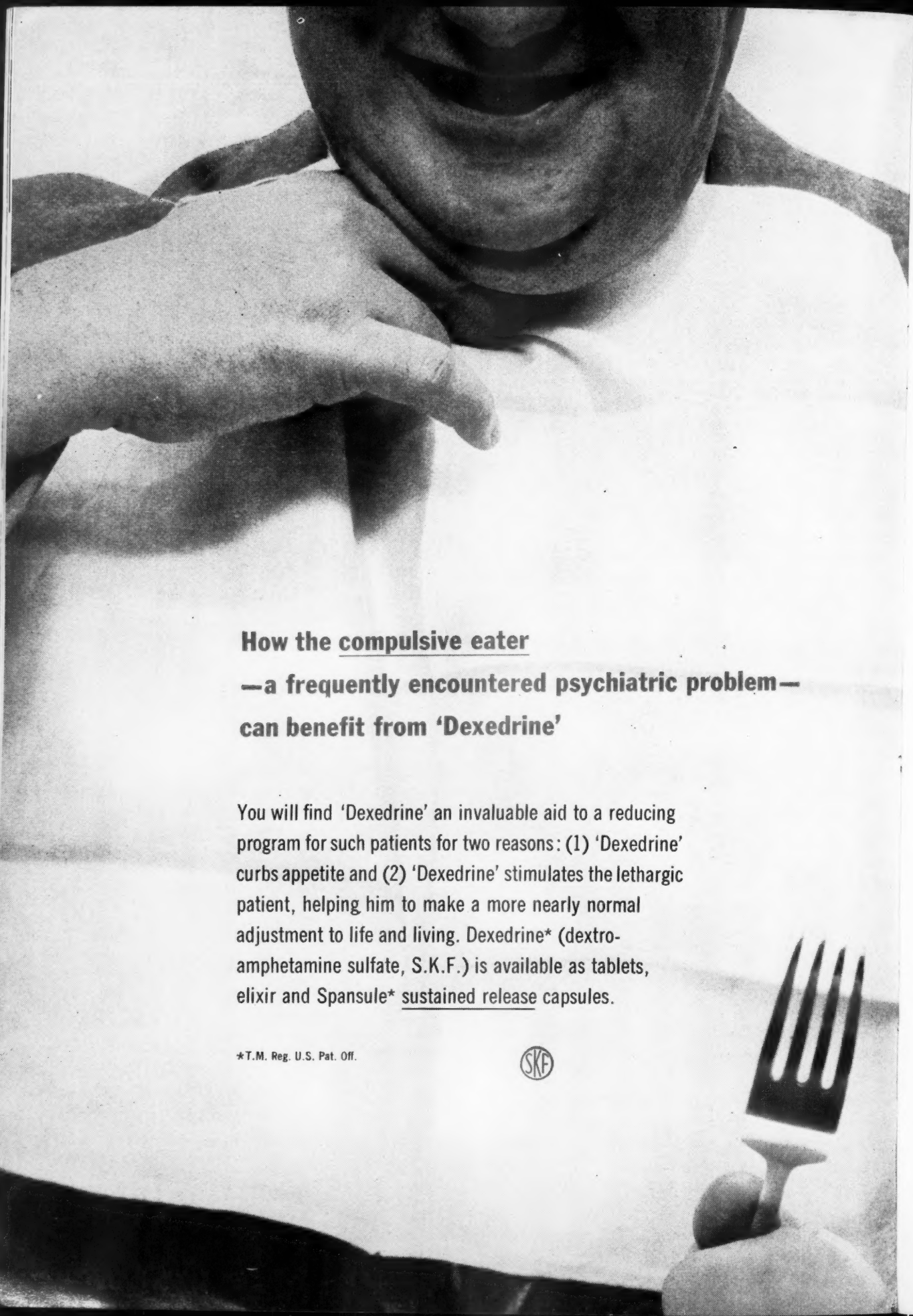

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DISEASES *of the* Nervous System

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

Peripheral Neuropathy Associated With Multiple Myelomatosis and Amyloidosis

Report of a Case

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LAWRENCE W. DUMAS, M.D., E. H. RENTSCHLER, M.D., and KENNETH M. EARLE, M.D.

Peripheral neuropathy associated with multiple myelomatosis has been reported in the literature at least 10 times as pointed out by Clarke. We have accepted the cases in Clarke's review as being proven cases of neuropathy existing with myelomatosis. Presence of amyloidosis was noted in three of these cases as summarized in Table I. We wish to describe another case of peripheral neuropathy associated with multiple myelomatosis in which the association of amyloidosis was proven by special staining of sections of the involved tissue.

Case Report

C.J.G. (UH-2579-I), 39 year old Negro male.

First hospitalization 2-11-52—3-21-52.

Chief Complaint: Numbness of the lower extremities and hands and extreme weakness.

Present Illness: In the summer of 1950 patient had experienced onset of low back pain with radiating sharp shooting pains down the posterior thighs to the knees. The symptoms increased in severity to the extent that the patient had to quit his job as clothes presser. There were no bladder, bowel, motor or sensory changes at this time. Coughing, sneezing and straining made his low back pain worse with no effect on the radiating pain.

In April 1951 he was seen by an orthopedist who noted compression of the fourth lumbar vertebral body, which was felt to be more typical of an inflammatory process than anything else. Positive blood serology was noted at this time so syphilis was favored as the etiological factor. Spinal tap or other diagnostic procedure was not done at this time. Vertebrae L-3, L-4, L-5 and the sacrum were fused at operation, and the patient was kept in a body cast for four months at bed rest.

One week prior to removal of the body cast the patient first noted difficulty in moving his toes, followed by weakness of his feet, legs and thighs. Coincident with this, numbness of his feet and legs was noted as well as sharp shooting pains of the legs. Three weeks later he noted onset of weakness of both hands with numbness and tingling of hands and forearms.

At the time of admission to the University Hospital on 2-11-52, the weakness and numbness of his lower extremities had progressed so that he had not been able to move his toes and feet for some time and he had been unable to perceive sensation in the feet and lower legs. He had been unable to have a penile erection for six months prior to admission. No bowel or bladder difficulty had been noted.

Family History: Father had hypertension and died of heart disease at age of 54. Mother had diabetes mellitus and died at age 57. Seven brothers living and well. One brother has diabetes mellitus.

Past Medical History: Influenza at age 5 years. Gonorrhea at age 15 years. Syphilis diagnosed by positive blood serology during World War II. Antiluetic therapy was given at that time. Married in 1943—no children.

Review of Systems

Eyes—Blurring of vision in right eye for several weeks prior to admission.

Ears—Tinnitus on right side for a few weeks prior to admission.

Cardiorespiratory—"Asthma for several years."

Dietary intake appeared to be adequate. No history of alcoholism. Smoked a pipe occasionally. Otherwise review of systems contributed no significant information.

Examination: Blood pressure—104/70. *Pulse*—80/minute—normal sinus rhythm. *Respiration*—20/minute. *Temperatyre*—98.8° F. (oral). *Height*—70 inches. *Weight*—150 lbs.

General: Patient appeared chronically ill, being poorly developed, poorly nourished, with evidence of weight loss. There was no evidence of distress of any kind.

The significant physical and neurological findings were as follows:

Back—Midline scar from lower thoracic region to

From University of Texas Medical Branch Hospitals, Galveston, Texas.

upper sacral region. Oblique scar over left posterior iliac crest region.

Eyes—Right optic disc margin was indistinct. No other abnormality noted.

Mental Status—No abnormality noted.

Cranial Nerves—All intact.

Motor: Lower extremities. Atrophy bilaterally from knees down. Toes and feet fixed in plantar flexion position. Bilateral foot drop previous to admission was implied by this finding. Inability to move toes and feet. Flexion at knees was fairly good. Upper extremities—Intrinsic muscle atrophy of hands and atrophy of forearm musculature. Weakness of all movements of upper extremities except at shoulder joints. Poor anal sphincter tone.

Cerebellar—No nystagmus.

Sensation: Pain—Impairment to pin prick over both feet and toes and lateral aspect of both legs and of all fingers and hands to the wrist level.

Motion and Position—Impaired in toes and fingers and in right foot.

Vibratory—Impaired in lower extremities and in hands to wrist level.

Testing over vertebral spines showed impairment below T-10 level.

Reflexes: Deep—All absent. Superficial—Abdominal and cremasteric reflexes could not be elicited. Plantar responses could not be elicited.

Laboratory Studies

Urinalysis: Specific gravity—1.015. Reaction—acid. Albumin—faint trace. WBC's—2-6/high power field. Bence-Jones protein—not present.

Hemogram: Hemoglobin—14.4gm%. RBC—5.25 million with 0.7% reticulated. WBC—8,500 (PMN—70%; PME—1%; L (small)—20%; Monocytes (active)—9%). Platelets—546,000. Hematocrit—43.5%. MCV—82.8 cubic microns. MCH—27.6 gamma gamma. MCHC—33%. ESR—43 mm/hour (Wintrobe, corrected).

Total Serum Proteins—6.3 gm% with A/G of 3.6/2.7.

Blood Calcium—8.3 mgm%.

Phosphorus—5.8 mgm%.

Acid Phophatase—1 Gutman unit.

Alkaline Phosphatase—1.6 Bodansky units.

Blood Serology: Kolmer—Positive 1:20. Kahn—Positive.

Blood Agglutination Studies: Negative for E. typhi H, E. typhi O, Paratyphi A, Paratyphi B, Prot. OX-19, Brucella, Tularemia.

Cerebrospinal Fluid Examination: Protein—141 mgm%. Kolmer—Negative. Lange—55554322. No cells.

Skin Tests: Tuberculin—negative. Coccidioidin—negative.

Histoplasmin: 1.0 cm. wheal with 7 mm. induration surrounding it on all sides.

Blastomycin: 1.5 cm. wheal with 1.0 cm. induration surrounding it on all sides.

Diagnostic Procedures

Roentgenograms: Cervical and dorsal spine: normal.

Lumbar Spine: Almost complete collapse of body of L-4 vertebra with the adjacent interspaces in good alignment. Soft tissue calcification around L-4. Pedicles of L-4 destroyed. Bony graft extending from L-2 to S-1 vertebrae with maintenance of bodies in good position.

Chest: Cystic lesion in third right rib posteriorly. Otherwise not abnormal.

Skull: 2 cm. diameter area of decreased density surrounded by sclerotic markings in right parietal region.

Myelogram: Showed slight symmetrical narrowing of the dural sac at the level of L-4. No abnormality of the thoracic, cervical or sacral regions was noted, and the remainder of the lumbar region was not abnormal.

Neurological consultation was obtained and it was felt patient's clinical picture was that of peripheral neuropathy with etiology not known.

Biopsy specimen was obtained from the body of vertebra L-4 via an abdominal extraperitoneal approach. The region of the body of the vertebra was noted by the surgeon to be soft, brownish-red in color, and markedly vascular. Microscopic examination of the biopsy specimen was reported as revealing a "uniform replacement of normal tissue by immature and mature plasma cells typical of myelomatosis."

Patient was discharged from the hospital following healing of his abdominal wound. He was given antiluetic therapy with an adequate amount of penicillin prior to discharge.

Readmission 5-12-53—5-23-53

Interval Note: There had been no significant change in his status except for occasional mild shortness of breath. He complained of tingling sensations in his arms and legs which were aggravated by cold weather.

X-rays of the skull, chest and lumbar spine showed no change as compared to previous examination.

Physical examinaton was essentially the same as that of first admission. Patient was instructed with regard to physiotherapy and discharged from the hospital.

Final Admission 2-23-56

Interval History: Patient had had shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, and edema of the lower extremities and genitalia as well as ascites for about six months prior to this admission. The "asthma" had persisted. He also had suffered from post-prandial precordial pain lasting about one hour, radiating through to his back and scapulae and associated with occasional bouts of tachycardia and irregular heart beats. He had been receiving medication and injections for the edema which were only mildly effective.

He had complained of dysuria and oliguria before the onset of his abdominal swelling. There had been no urinary incontinence, but there had been nocturia of 4-6 times for six months prior to admission. He

had experienced frequent episodes of fluid rising from his stomach to his throat and mouth that caused intense burning and a sensation of "rawness" in his throat. This was severe enough to cause temporary loss of taste and other intra-oral sensation. He had suffered from right-sided headaches occasionally, at which times he seemed to be blind in his right eye, and "it felt like it would pop out of my head."

There had been an occasional temperature elevation to 100° F. orally. He had had anorexia for five months prior to admission and frequent bouts of 3-4 loose, watery stools per day since 1953 along with fecal incontinence. Muscular wasting and weakness and limitation of motion of the upper extremities had progressed to the point that he could feed himself only with his right hand. His skin had gradually become tight and swollen throughout his body. Transient subcutaneous "nodules" had been appearing for four or five months prior to this last admission.

Examination: Blood pressure—130/80. Temperature—99° F. Pulse—88/minute. Respirations—24/minute. Height—70 inches. Weight—160 pounds.

General: The patient was an alert, cooperative negro male appearing younger than his stated age of 43 years. He appeared chronically ill. He was rather orthopneic and his respirations were shallow and mostly diaphragmatic. There was generalized muscular wasting and the muscles seemed to have a doughy consistency.

Skin: Anasarca was present. The skin was glabrous, tight, inelastic and edematous with loss of its appendages. There was a 5 x 5 cm. soft nodular mass at the left anterior axillary line over the 7th rib (which disappeared overnight). A few purpuric spots were seen. There was no macroglossia or evidence of amyloid infiltration of the skin. The mucous membranes were quite pale except for the gums and lips which appeared pink, and they showed no evidence of amyloid nodules.

The fingernails exhibited koilonychia and loss of the lunulae. There was scrotal and preputial edema. Striking the skin would produce soft, doughy nodule which would disappear in a few minutes.

Eyes: No abnormality noted.

Chest: The thoracic cage had an increased anteroposterior diameter and exhibited very little respiratory excursion, seeming to be "frozen" in inspiration. Breathing was mostly diaphragmatic. The diaphragms were markedly elevated. There were diffuse, moist rales at the lung bases. There was evidence of fluid present in the right chest. The heart occupied a horizontal position and was not enlarged. There was an occasional premature beat. There was a Grade I apical systolic murmur. The mitral first sound was less than the mitral second sound. The aortic second sound was tambouric and less than the pulmonic second sound.

Abdomen: There was marked ascites and scrotal edema. The liver, spleen and kidneys were not palpable, possibly due to the ascites, but the spleen was thought to be enlarged to percussion. The veins on the abdominal wall were distended, and the flow of blood in these above the umbilicus was cephalad.

Rectal: Prostate was small. Anal sphincter tone was poor.

Motor Status: Changes were similar to those seen on previous admissions with the additional fact that the wasting was more severe, and fixation and limitation to passive movement at the joints was more marked. There was bilateral foot drop and the toes were fixed in plantar flexion. He had bilateral thenar and hypothenar atrophy as well as pectoral and intercostal muscle atrophy.

Sensory status, reflex status and cranial nerves were as seen at previous admissions.

Laboratory Studies

Urinalysis: Reaction—acid. Albumin—1 plus. WBC's—2-3/hpf. Rare hyaline cast. Bence-Jones Protein was not present.

Hemogram: Hemoglobin—7.7 gm%. Total RBC—2.88 million, with 1.2% reticulated. WBC—5000 (PM N (active) 46%; stabs 2; lymphocytes (small) 41%; lymphoblasts 1%; monocytes (active) 10%). Platelets—478,080. Cell volume—25.5%. MCV 89 cubic microns. MCH 26 gamma gamma. MCHC 30. Slight hypochromia and strippling.

Bleeding Time: 2 minutes.

Clotting Time: 3 minutes and 10 seconds.

Prothrombin Time: 100%.

Bone marrow showed hypercellularity. There was marked stimulation of the myeloid elements with a definite left shift. There was an increase in the number of plasma cells, a few of which were immature. There were a few immature unidentified cells. Mature lymphocytes were also increased in number. The erythroid elements showed marked stimulation, especially at the normoblast level. The megakaryocytes were increased in number and showed a definite left shift.

Paper electrophoresis of the patient's hemoglobin revealed the characteristic AS pattern of sickle cell trait.

Blood Chemistry: Serum chlorides—99meq/L. CO_2 combining power—24.4 mm/L. Total serum proteins—6.2 gm% with A/G 3.2/3.0. Serum calcium 4.0 meq/L. Acid phosphatase—2 Gutman units. Alkaline phosphatase—0.7 Bodansky units. Phosphorus—2.0 meq/L. Serum potassium—3.6 meq/L. Serum sodium—146 meq/L. Total serum cholesterol—128 mgm%. NPN—45 mgm%. Fasting blood sugar—70 mgm%.

Cerebrospinal Fluid Examination: Kolmer—negative. Glucose—68 mgm%. Cells—25 RBC and O W BC/mm^3. Protein — 154 mgm%. Chlorides — 115 meq/L.

The Congo Red Test was performed and 27% of the dye disappeared while 73% of the dye remained in the blood after one hour. The urine appeared normal.

Serum protein electrophoresis was as follows:

Albumin: 35.1% (decreased).

Globulin: Alpha 1—5.7% (very slightly increased).

Alpha 2—8.5% (normal). Beta—13.7% (normal). Gamma—37.0% (increased.)

The gamma-globulin fraction probably contained some myeloma protein; in fact, about 27% of the total protein, or approximately 75% of the gamma-globulin, was composed of this.

Diagnostic Procedures

Punch biopsy of the kidney was attempted but the amount of tissue obtained was insufficinet for diagnosis, showing only a few tubules, which did not demonstrate amyloid with the Congo Red stain.

Biopsy of skin over one of the nodules showed chronic inflammation but no amyloid was present.

Venous pressure in the left antecubital vein was 13 cm. of water.

Arm-to-tongue circulation time of the blood with sodium dehydrocholate was 13 seconds.

Roentgenograms

Chest: The lesion of the third rib appeared to be more advanced as compared to the last previous examination. Pleural fluid was thought to be present on the right side.

Lumbar Spine: There was little change from the last examination except for calcific densities about the bodies of vertebrae L-3, L-4, and L-5.

Skull: Marked hyperostosis frontalis interna and a thickened, dense-appearing diploic space of the calvarium were present. There was increased sclerosis in the right parietal lesion seen on previous examination.

Intravenous urogram revealed excretion of the dye bilaterally but the visualization was inadequate for accurate evaluation of the collecting systems.

Several x-ray films of the upper extremities using soft tissue technique revealed no evidence of calcific deposits.

Electrocardiogram revealed a sino-atrial rhythm with a ventricular rate of 100/minute. The electrical axis was a plus 45°. The voltage was rather low. PR interval was 0.18 seconds, QRS 0.08 seconds, and QT 0.34 seconds. There was myocardial ischemia anterolaterally and posteriorly and a premature atrial beat. There was a suggestion of left ventricular hypertrophy.

Course in Hospital

The patient was treated with bed rest, multivitamins, coronary vasodilators, diuretics and adequate diet. He had a progressively down-hill course and expired on 3-2-56. Permission for autopsy was denied.

The old blocks of tissue obtained from the original biopsy of the fourth lumbar vertebra were reexamined utilizing various techniques. Histological examination of tissue from the fourth lumbar vertebra removed on 3-14-52 stained with H & E had revealed multiple myeloma. Recuts of these blocks of tissue stained with Congo Red revealed pink-staining, hyaline material within the cytoplasm of mononuclear cells and small masses of similar material in the stroma. This material stained the same as a control slide of amyloidosis. Crystal violet stains were positive for amyloid in this material and in control slides, but this stain was less characteristic than the Congo Red which had been negative on a piece of skin from the left flank removed on 2-28-56. They had also been negative on a needle biopsy of the kidney 3-2-56 and considered too small for diagnosis since only a few tubules and no glomeruli were present in the specimen.

Discussion

The peripheral neuropathy in this case was typical and was recognized as such when the patient was first seen and the accompanying diagnosis of multiple myeloma made. However, the association of these two conditions was not known to those first seeing the patient, and it was not until his final admission that this was discovered and amyloidosis searched for. This investigation was initiated after seeing Clarke's report.

The features of myelomatous neuropathy and amyloidosis, clinically, may be mutually confusing. In this case report we find this is so to a variable extent. In our patient the only sites where amyloid was demonstrated were in the cytoplasm of mononuclear cells and in the surrounding stroma in the biopsy specimen from vertebra L-4. However, clinically, one can marshal strong support for the diagnosis of an associated primary systemic amyloidosis in this patient. (He exhibited no evidence of tuberculosis or chronic suppurative disease which one finds with secondary amyloidosis.)

In primary systemic amyloidosis the sites of predilection for amyloid deposition are cardiac, skeletal and smooth muscle; other areas may be variably involved. The main feature in most of the cases is the combination of cardiac failure, chronic diarrhea and peripheral neuropathy. In our patient skeletal muscle, gastrointestinal and skin involvement, peripheral polyneuropathy of undetermined etiology, pulmonary, coronary and cardiac insufficiency, with definite evidence of myocardial damage, abnormal serum proteins, and lack of macroglossia cannot be questioned.

The splenomegaly, vascular changes in all extremities during cold weather, involvement of the right optic and auditory nerves, and skin "nodules" were not objectively substantiated. The skin "nodules" were probably

due to myoedema. There was a lack of conspicuous hyperglobulinemia, which is usually the case in multiple myeloma associated with amyloidosis (Cecil and Loeb).

Cirrhosis of the liver and renal amyloidosis were not ruled out, but our evidence does not allow us to entertain these diagnoses in this patient. It is well known that these disorders may be confused with congestive heart failure, but in our opinion chronic congestive heart failure was the principal cause of his anasarca rather than renal and/or hepatic amyloidosis.

Various etiological factors have been suggested as the cause for neuropathy in myelomatosis, including toxic influences (Scheinker), hyperglobulinemia (Berlin), production of toxic phenomena by Bence-Jones protein (Magnus-Levy), and anemia as the provocative factor (Davison and Balser). There appears to be no definite proof that myelomatuos infiltration of peripheral nerves, spinal nerves or cranial nerves occurs. In Scheinker's case, the only one in which there was a pathological examination of the nervous system, parenchymatous degeneration was seen in the spinal roots. With regard to the etiology we would like to present the following postulation:

In multiple myeloma patients the "amyloid" is produced by the myeloma or plasma cells since it is known that these cells are not phagocytic, yet their cytoplasm does contain "amyloid." This abnormal material may be a precursor of cryoglobulin(s) or it may be the cryoglobulin itself. This material may then cause vascular insults to the vasa nervora by "precipitating" in them with subsequent "amyloid degeneration" of this substance and result in abnormal fragility of these tiny blood vessels to produce the neuropathy. It could also cause injury to nerves

TABLE I

Cases of Neuropathy Associated With Myelomatosis

Case No.	Author	Date	Sex	Age	Presenting Symptoms	Total Survival	Roentgenograms	Spinal Fluid Protein mgm%	Outcome	Amyloid
1.	Scheinker	1938	M	38	Pigmented skin, numb toes	14 mos.	———	Normal	Death (autopsy)	Not mentioned
2.	Berlin	1946	M	64	Temperature changes and aching in feet	9 mos. (plus)	Spine, skull, etc., normal	61	?	Not mentioned
3.	M.G.H. Case #32231	1946	F	51	Aching and burning in finger tips	6 mos.	Normal	Normal	Death (autopsy)	Present
4.	White & Tillinghast Case 3	1950	M	59	Chronic diarrhea	?	Multiple granular bony lesions	———	?	Not mentioned
5.	Madonick & Solomon Case 6	1953	M	53	Paresthesias of fingers and toes	8 mos. (plus)	———	212	Death (autopsy)	Not mentioned
6.	Madonick & Solomon Case 8	1953	M	58	Shoulder pain	12 mos. (plus)	Normal	71	Death (autopsy)	Of tongue
7.	Madonick & Solomon Case 10	1953	M	53	Skin nodules	8 mos. (plus)	———	72	Death (autopsy)	Not mentioned
8.	Madonick & Solomon Case 14	1953	F	59	Pain in right arm	2 yrs. (plus)	Normal	Normal	Death (autopsy)	Generalized
9.	Estes & Millikan	1954	F	43	Low back pain	4 mos. (plus)	Normal	200	?	Not mentioned
10.	Clarka	1955	M	66	Paresthesias limbs and trunk	15 mos.	Normal	25	Death (no autopsy)	Not looked for
11.	Present Case	1956	M	43	Low back pain, paresthesias and weakness all extremities	5 yrs. (plus)	Collapsed L-4, cyst right third rib, skull lesion	154	Death (no autopsy)	Present

by infiltration and/or compression due to the fact that water and protein are physicochemically implicated in one another. Their relationship may be easily upset by various physical disturbances, particularly temperature changes, which could result in transvascular migration, "precipitation," and then mechanical interference with surrounding tissues. The "precipitation" of the "cryoglobulin" may, in part, account for the lack of conspicuous hyperglobulinemia in these patients, and it may be the substance which is responsible for the alteration in the staining characteristics of "amyloid" in patients with primary systemic amyloidosis as compared to patients with other types of amyloidosis. Possible support for this idea may be found in serum protein electrophoretic studies, for, by utilizing this procedure it has been shown that cryoglobulin(s) has the same mobility as gamma-globulin. It will be recalled that our patient had normal total serum protein but increased gamma-globulin, 75% of which was thought to be "myeloma globulins" (quite possibly cryoglobulin[s]). Some other abnormal protein fraction(s) may be implicated, however. Study of cases in which this association of neuropathy and myelomatous disease is noted may settle this problem and perhaps confirm or deny the clinical suggestion that amyloidosis may be the cause of the peripheral neuropathy.

Amyloid disease is always included in a listing of the differential diagnosis of peripheral neuropathy in textbooks of neurology, and it may be that in multiple myeloma cases it is the ultimate cause of the neurological involvement. It is regretable that a postmortem examination was not obtained in this case, but it is hoped that this report will help stimulate investigations in this direction in subsequent cases.

There does not appear to be anything peculiarly characteristic of the neuropathy in myelomatosis to distinguish it clinically. This emphasizes the necessity of investigation for the possible existence of myelomatosis (and amyloidosis) in unexplained cases of peripheral neuropathy. Any case of known amyloidosis with neuropathy should be investigated as a possible case of multiple myelomatosis since it is mentioned (Snapper, Turner and Moscovitz) that in cases of myelomatosis with amyloidosis the bone roentgenograms may be normal.

Summary

A case of peripheral neuropathy in association with multiple myelomatosis and amyloidosis is presented. Attention is called to the possibility of amyloidosis as the etiology of the peripheral neuropathy seen with myelomatosis.

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Reactivity of Brain Tissue to Intracranial and External Electrotherapy

JUAN NEGRIN, JR., M.D.

For some time we have been developing a method to treat mental illness and related conditions by administering an electric current directly to the brain through intracranially placed electrodes.[1] Our technique is based on the assumption that an electric current may give better results if received directly by the specific brain areas than if it reaches the brain in a diffuse manner as was generally supposed to happen with external electrotherapy. Preliminary reports in the medical literature reveal that others, with individual variations in technique, are also using electric current applied directly to the brain for therapeutic purposes. Among those active in this field are the groups of Delgado and colleagues (Proc. V. Int. Neur. Cong., 1953), Robert Heath (Studies in Schizophrenia, Harvard Univ. Press, 1954) and Bickford and associates (Bull. Mayo Clinic, 1953). Lawrence Pool has recently confirmed the therapeutic effect of an electric current when applied directly to the brain in cases of intractable pain (Proc. N. Y. Soc. of Neur. and Psych., 1954).

Improvement of mental symptoms and syndromes with this procedure, when external electrotherapy failed, was strong subjective evidence in favor of this hypothesis. The comparative study of the cerebral electrical activity, before and after intracranial and external electrotherapy, seemed to be a way to obtain the objective evaluation desired. This was done with electroencephalographic recordings.

The purpose of this paper is: a) to summarize findings that seem to illustrate the difference in reactivity of the brain to an electric current when applied directly and when applied through the external surface of the scalp; and b) to present observations demonstrating that the reaction of the brain varies with the electrotherapy used.

Read at the Electroshock Research Association meeting, Chicago, April 1956.

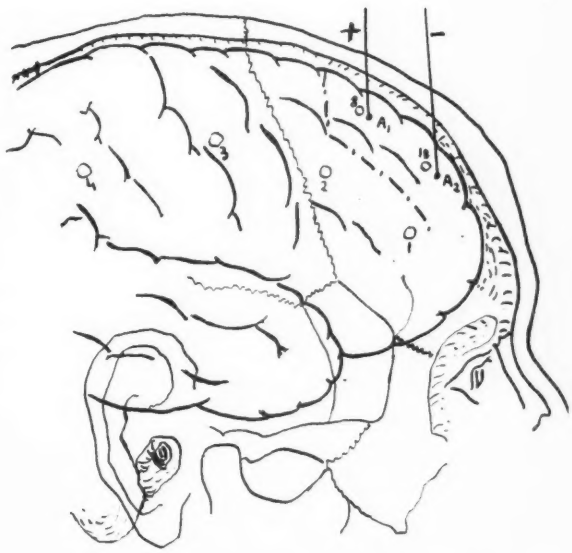

Fig. 1. Schematic drawing to show the intracranial electrode placements (A1, A2) to be connected to the source of the electric current (C) after a selective undercutting (.—.—.) of the frontal lobe was done. Electroencephalograms using (O) scalp electrodes (8, 18, 1, 2, 3, 4) and (.) intracranial electrodes (A1, A2) were taken before and after the current was applied.

Materials and Methods

Observations were carried out on chronic deteriorated psychotics who had a standard psychosurgical operation followed by external and internal electrotherapy. Another group of patients was treated with a combination of intracranial and external electrotherapy, but without prior psychosurgery. For intracranial therapy the electrodes were left in position, after closure of the scalp, for periods varying from two to over ten weeks. The electrodes were placed 1) cortically (subpially) over the cortex above the undercut area (Fig. 1) and in other subpial regions of the brain; 2) in the gray and white matter of the cerebral hemisphere and 3) in different parts of the pituitary gland (Fig. 2, 3). For external electrotherapy, the "uni-polar" method was also used, one electrode on the right ankle and the other over several areas of the external surface of the scalp (Fig. 4).

E.E.G.'s were taken before and after surgery and prior and subsequent to each electrical treatment. Standard scalp electrodes were used, combined with intracranial (subpial, subcortical and hypophyseal) electrodes.

Fig. 2. Skull X-ray. Anterior posterior view to show the cerebral and hypophyseal electrodes in position.

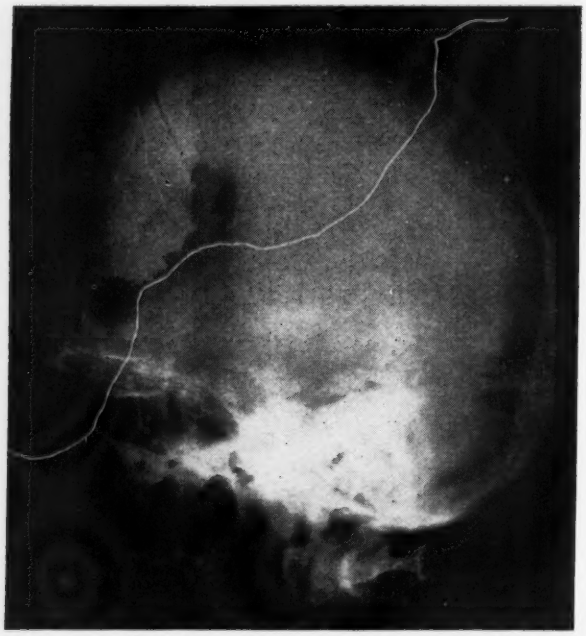

Fig. 3. Skull X-ray. Lateral view showing the cerebral and hypophyseal electrodes in position.

Results

In the brief description of results that follows, only the more outstanding features will be mentioned.

Observations after Psychosurgery Followed by External and Intracranial Electrotherapy

At different post-operative periods of time, electroencephalographic studies were done as described above. E.E.G.'s taken before and after external electrotherapy (Fig. 5, 6) showed no appreciable change even though one of the electrodes was placed over the scalp covering and just above the undercut part of the frontal lobe. However, when the same type of current was directed to the undercut brain tissue through intracranial electrodes, a paroxysmal discharge was demonstrated on the E.E.G. (Fig. 7) although no clinical convulsion was visible.

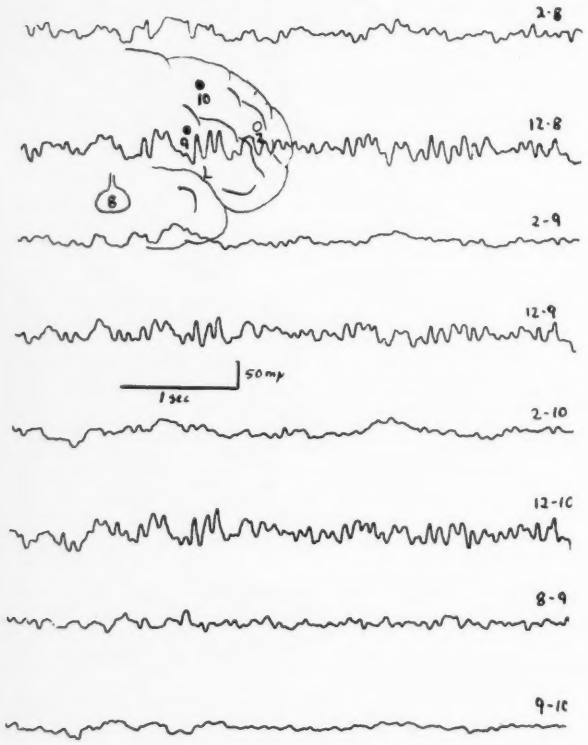

Fig. 4. E.E.G. before intracranial application of an electric current. Scalp electrode 02; subpial electrodes 10, 9; hypophyseal electrode 8. There was no change in the spontaneous E.E.G. after a current was applied by way of "external" monopolar or bipolar methods.

These findings seem to indicate that, at least under the above circumstances, the brain responds to an electric current applied intracranially and not to the same current externally applied.

It is not our intention to discuss in detail the hypersensitivity of the isolated cortex to an electric current. However, it seems from our observations that in the human a partially isolated cortex responds to the current we used with a paroxysmal epileptoid-like discharge. Such response could not be obtained when the same current was applied for the same length of time through electrodes placed in cerebral structures outside the partially isolated brain. Similar observations have been reported in animals.[2] It appears also that the paroxysmal discharge obtained under these circumstances spreads to the rest of the brain through the bridge connecting the partially isolated cortex with the remaining cerebral hemisphere.

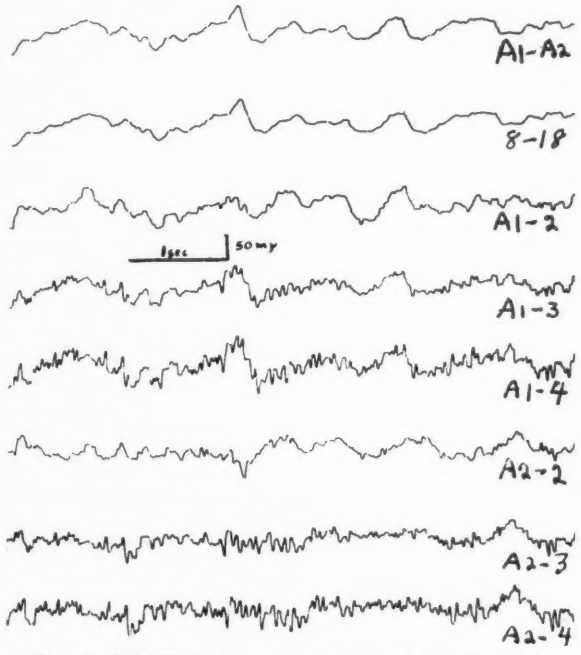

Fig. 5. E.E.G. before standard "external" electrotherapy methods (monopolar and bipolar). (See diagram on Fig. 6 for position of electrodes.)

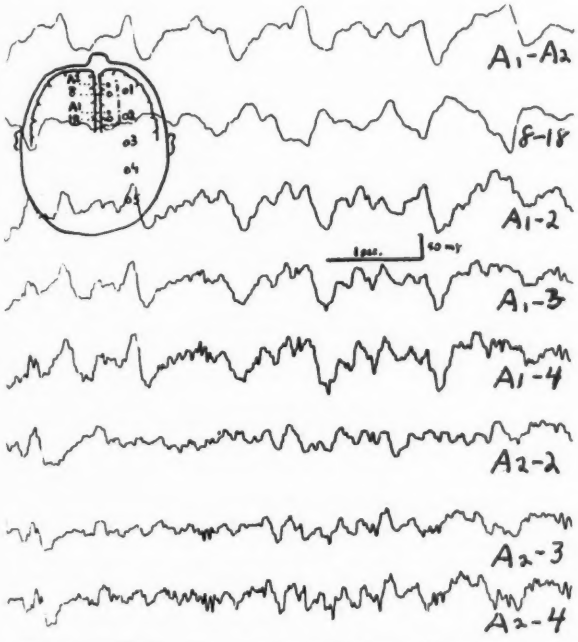

Fig. 6. E.E.G. after "external" electrotherapy (unipolar and bipolar). No significant change from Fig. 5.

Observations After Electrotherapy Without Prior Psychosurgery

A current was sent through one subpial and one hypophyseal electrode (Fig. 8a, c). The polarity of the electrodes was reversed and the same current was again sent through. When the subpial electrode was positive, sustained high amplitudes and fast spikes were obtained (Fig. 8b). When the polarity was reversed and the subpial electrode was negative, intermittent, periodic,

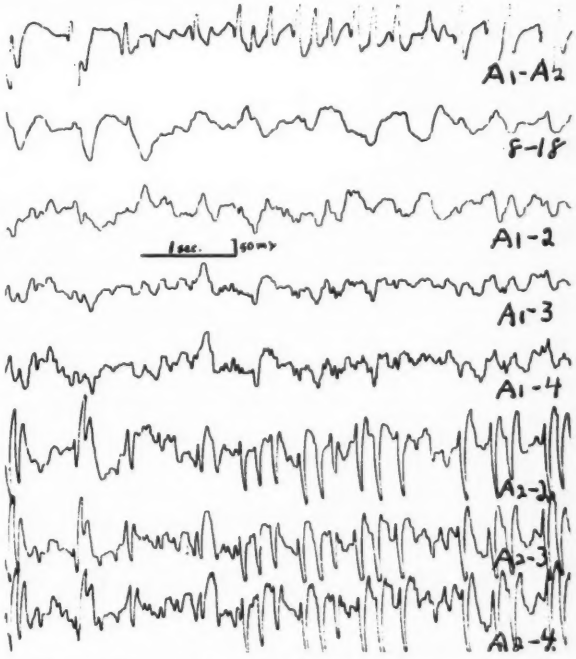

Fig. 7. Paroxysmal discharge subsequent to the application, through intracranial electrodes, of the same electric current used before E.E.G. of Fig. 6. See Fig. 6 diagram for position of electrodes.

well-modulated bursts were recorded (Fig. 8c). The same step was repeated, this time using one subpial electrode and another electrode on the right ankle (Fig. 8a, b). Again the electrical activity revealed sustained high amplitude, fast frequency spikes (Fig. 8d). Once more, when the polarity was reversed, the tendency to periodic bursts was noted (Fig. 8c). When the same type of current was applied during the same period of time externally through monopolar or bipolar methods, no rsponse in the cerebral activity was noted, as evidenced by unchanged E.E.G.'s before and after its application (Fig. 4).

The above findings suggest that the reactivity of the brain at each electrode site debends on the polarity of the electrode. The two types of activity, fast sustained spikes and periodic bursts of spike waves are specific for each electrode for the same polarity. Either one was obtained at will simply by using the polarity of choice when the current was administered. These electrical findings have been present when one electrode is placed subpially, but regardless of whether or not the other is placed hypophyseally or externally (ankle). The amplitude of the discharge was smaller as the distance between the electrodes increased, so that the lowest amplitude was obtained by combining the ankle electrode with the subpial. That the distance between the electrodes is the factor affecting the amplitude of the response seems further confirmed when by separating two subpial electrodes by a dis-

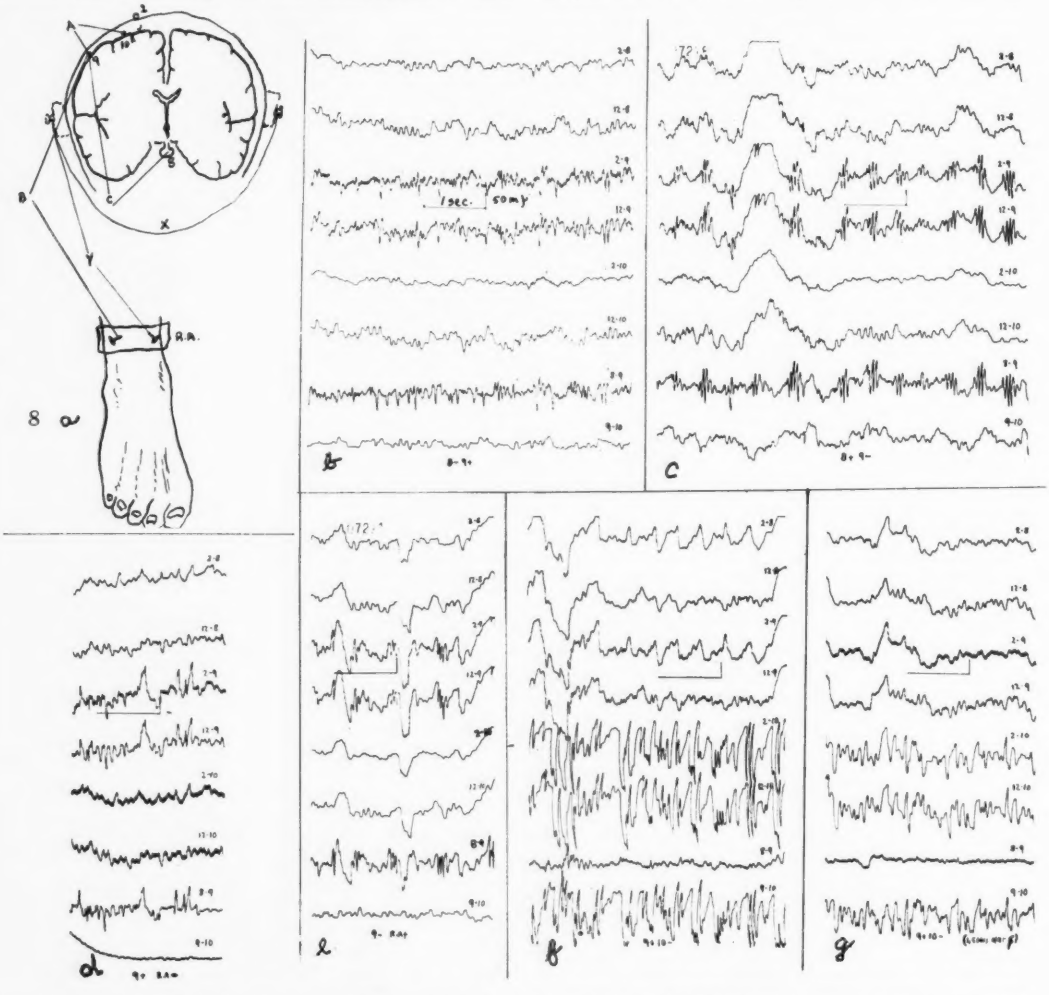

Fig. 8. Reactivity of brain tissue to different technics of intracranial electrotherapy. The electrical response varies, depending on the polarity and distance between the electrodes, as evidenced by the above E.E.G.'s.

8a. Combinations used for intracranial and "external" administration of an electric current.

A. Both subpial electrodes (9-10).
B. One subpial (9) and right ankle (RA).
C. One subpial (9) and one hypophyseal (8).
X. Standard "external" bipolar.
Y. Standard "external" monopolar.

tance of 3 cm. the highest amplitude of the burst is obtained (Fig. 8f, g). It appears that the energy concentration per unit volume is a significant determining factor for E.E.G. response as evidenced by our recordings. It is, therefore, possible to utilize a single cerebral electrode with an externally placed indifferent electrode if found desirable to apply concentrated local therapy at low energy levels for long periods of time, or, if it is desired, to use extremely high energy levels at local areas without running the risk of too great heat concentration in small volumes. If the electrodes are close together, so that the full energy is concentrated in the smallest vloume, we have the maximum E.E.G. response. When the electrodes are widely separated, we have the minimum response although the same pattern is maintained.

The great usefulness of intracranial electrotherapy when maximum activity in a local area is desired appears, therefore, to be obvious. In other words, we now have available with the existing tools a method of treating selected volumes of the brain either with extremely high concentrations of energy in a very small and limited volume with maximum activation, or a variation of this technique using simply a local electrode with a current pathway leading to a distant "indifferent" electrode (monopolar system), and utilizing high volumes of current to result in maximum concentration of energy for a small local area without the high heat concentration of the first method. It is also possible by using the "long distance" electrode placement and low volume of current to prolong the stimulation for reasonably long periods to effect gradual build-up of changes.

Discussion

Intracranial electrotherapy has been used with satisfactory results in problems of mental illness. It has also given good results when used to relieve intractable pain. At this time it is not intended to present the clinical evaluation of intracranial electrotherapy which we feel is indicated for patients who do not improve or recover after insulin shock and external electrotherapy. Admittedly, brain functions change in a different manner when an electric current is applied directly to the brain than when applied indirectly through the surface of the scalp. Perhaps this is the reason for the improvement obtained with intracranial electrotherapy when the external methods fail.

Our electroencephalographic studies reveal that the electrical response of the brain differs with internal and external electrotherapy. When the polarity of the electrodes is reversed, the electrical activity obtained at each electrode point changes. The distance between the electrodes seems to be a factor in the amplitude of the electrical discharge. If we assume a correlation between the degree of change in mental function and the intensity of a particular electrical response (as measured by the amplitude), a logical deduction would be to consider that the intensity or severity of the change in previously existing or newly created mental function would depend on the amplitude of the discharge and, therefore, on the distance between the electrodes. Should this be further confirmed, the distance between the electrodes may be another element to be considered for therapy.

One more factor that may deserve a comment is our placement of hypophyseal electrodes. These were used with the intention of adding neuroendocrine components to further therapeutic results. Clinical observations on mental and metabolic changes under these conditions will be the subject of a future report.

Summary

The reactivity of the brain to intracranial and external electrotherapy is studied by way of E.E.G. techniques. The electrical response of the brain varies when a current is applied directly or through standard scalp electrodes. It is suggested as possible that a certain degree of correlation exists between the degree of change in mental function and the amplitude of electrical discharge of brain tissue in response to intracranial electrotherapy. The reactivity of the brain seems to vary according to the polarity of the electrodes. The amplitude of the electrical response is in proportion to the distance be-

tween the electrodes. The polarity and distance between electrodes may be, therefore, a factor to consider in leectrotherapy. A brief reference is made to the application of an electric current of different paremeters directly to the pituitary gland to enhance the therapeutic results of intracranial electrotherapy.

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108 East 81st Street, New York, New York.

Prochlorperazine (Compazine) in Emotional Disturbances

LOUIS G. MCAFOOS, JR., M.D.

Extensive clinical trials to evaluate prochlorperazine as an antiemetic agent, conducted in this country and Europe, established the utility of the compound for controlling nausea and vomiting due to diverse causes.[1,2,3] Moreover, they indicated its relative safety. No serious untoward reactions such as agranulocytosis or jaundice were associated with its use. In addition to antiemetic activity, prochlorperazine possesses an outstanding ability to abolish conditioned-reflex response in animals, surpassing even chlorpromazine in this respect, without appreciably inhibiting cortical responsiveness.[4] This property of prochlorperazine suggested its possible clinical usefulness to alleviate the conflict-laden conditioning in man that so often plays a major role in neuroses and psychoses. Therefore, in May 1956, I undertook an evaluation of prochlorperazine in the treatment of anxiety and other emotional disturbances commonly encountered in general medical practice.

Material

Fifty-two patients who presented a variety of somatic complaints but had in common rapidly mounting tension, a disturbing uneasiness of mind, and ill-defined nervous feelings comprised the study group. These 14 men and 38 women ranged from 20 to 84 years, though most were between 35 and 55 years. Diagnostically, 33 had anxiety reaction; 6, psychophysiological reaction; 5, senile agitation; and 8, depressive reaction. Symptoms, except for the last diagnostic category, were typical of those seen in moderately ill psychoneurotics. The depression noted, however, appeared mild in that patients did not exhibit signs of suicidal preoccupation, but laconically presented complaints such as "tired all the time," "loss of interest in things," "not sleeping well," and "poor appetite" superimposed on an attitude of restlessness and easy perturbability. In only two patients, both of whom were arthritics, did emotional problems stem from their physical illness. In the others, complaints of headache, pre-cordial pain, vertigo insomnia, anorexia, epigastric distress, and non-specific musculo-skeletal pains seemed to result from their emotional problems.

Method

The extent of each patient's physical illness was determined by examination and laboratory studies, as indicated, to rule out organic disease as a cause for personality changes. At the time of examination, each patient was interviewed to determine the severity of his illness, the factors precipitating or contributing to it, and the prospects of his benefiting from supportive measures, such as reassurance, sympathy, persuasion, and encouragement. With the exception of five patients, the group seemed capable of being managed by such measures, when coupled with drug therapy to provide symptomatic relief. The exceptions, in contrast to the mild to moderate disturbances seen in the rest of the group, bordered on being ill enough to be committed to a mental hospital, but isolating them undoubtedly would have imposed a strain on their already overburdened personality and made matters worse.

All patients were started on prochlorperazine (5 mg.) tablets three times daily. Dos-

age was subsequently adjusted to maintain the patient in a calm, relaxed state without undue sedation. The usual maintenance dose was 5 mg., q.i.d. At the time of the study, the medicament was not commercially available so it was dispensed in my office. Patients were interviewed after a week's trial of the drug. Those who tolerated it or who appeared to benefit from taking it were continued on the drug, and subsequently seen every two or three weeks, depending on their progress and the need for further counselling. The depressed patients, however, were seen weekly or more often for short periods until it could be reasonably well determined that suicidal traits were not latent. Midway in the study, 11 of the patients initially given tablets were switched to prochlorperazine in sustained release Spansule capsules, to be taken once daily. This form contained 15 mg. of the drug incorporated in hundreds of tiny pellets coated with various thicknesses of a digestible film so prepared that it released part of the total dose immediately and the remainder gradually to sustain the initial therapeutic effect approximately twelve hours. Duration of treatment, using both tablets and Spansule capsules, ranged from three to sixteen weeks; three-fourths of the group received prochlorperazine for eight weeks or more. Blood studies were run periodically during the course of treatment.

Results

Results of treatment were graded according to the following criteria:

Excellent means the patient is essentially recovered, that is, he displays no overt symptoms, is generally benefiting from supportive counselling, functions well socially, and appears capable of resisting normally-occurring environmental stress. *Good* means the patient is symptom-free or relatively so, has made progress in gaining insight, and can face situational problems without undue or disabling distress. *Fair* means the patient is making a satisfactory adjustment but that his symptoms remain, though in decreased intensity, and shows some response to counselling. *Poor* means the patient shows no benefit from treatment or that troublesome side effects necessitated discontinuation of therapy.

Of 52 patients 44 showed a beneficial response to prochlorperazine: 17 *Excellent;* 22 *Good;* 5 *Fair;* 8 *Poor.* Improvement, when noted, usually occurred within one week's time, beginning as a reduction in tenseness and apprehensiveness. Physical complaints, such as headache and epigastric distress, subsided too, sometimes gradually, sometimes dramatically over a course of a few days, usually in relation to the chronicity of the complaint. With the subsidence of symptoms—which to some patients seemed the forerunners of insanity, heart disease, or cancer—mental outlook brightened markedly. They seemed, in general, more willing to talk about their fears, blows to self esteem, guilt feelings, frustrations, and other resentments to life. Four of the five patients on the verge of requiring hospitalization (two agitated seniles and two patients whose anxiety threatened to reach panic levels) responded sufficiently to prochlorperazine, becoming amenable to psychotherapy, and continued treatment on an ambulatory basis. The other patient, plagued with anxiety, was committed to a state hospital where she is progressing satisfactorily on chlorpromazine and her prognosis appears good. Patients given prochlorperazine Spansule capsules as maintenance therapy obtained day-long relief from their symptoms of emotional distress. A number of patients, mostly those going to business, volunteered their preference for this form of medication. They found it advantageous not to have to take medicine at work because it enabled them to avoid embarrassment.

Of the four types of patients presented in this series, those with anxiety reaction appeared to be helped most by prochlorperazine. In the main, their anxiety and resultant symptoms stemmed from environmental factors that they could not cope with, rather than from an underlying character disorder.

All experienced symptomatic relief when given prochlorperazine and, with supportive psychotherapy, showed progress in adjusting to their environment. Generally speaking, they seemed to regain the ability to relax, sleep better, and feel refreshed. Degree of improvement, quite naturally, depended on

the flexibility of the patient and his environment. One patient, a 46 year old man, had had a four year history of great tension and severe, daily recurrent headaches which became progressively worse to the point that he was disabled physically and socially, becoming irascible, irritable, and moody. Histamine desensitization, tried previously, had proved inadequate. After taking prochlorperazine, he reported feeling relaxed, was more inclined to discuss his domestic problems, resumed his job, and in four weeks of treatment, experienced only one headache. Less fortunate was a 37 year old woman whose anxiety, tension, and generalized gastrointestinal distress completely subsided until her husband, a philanderer, indiscreetly entered into an affair, causing an exacerbation of symptoms that, with the circumstances, proved unresponsive to further treatment.

A similar study in contrast occurred in the two arthritic patients, both middle-aged women, whose onset of anxiety was triggered by their physical illness, producing in them exaggerated fears of helplessness, almost to the point of panic. Neither had responded to steroid and salicylate therapy. Prochlorperazine was added to their regimen at the time when their complaints were intensified. In two weeks' time one patient showed a marked improvement in both physical and mental distress, and has maintained this improvement over a period of ten weeks. The other showed no improvement; perhaps, as several of her remarks indicated, she had found some advantages in her disability.

Those with a psychophysiological reaction, generally speaking, responded favorably to prochlorperazine. However, response was not immediately apparent and occasionally did not result until patients had been on the drug three weeks or longer. The slow progress in this group may have been due, in some measure, to the fact that the patients, unlike those in the other groups, strongly held that their symptoms of tension, weakness, and apprehension resulted from their physical illness. To suggest at the outset of treatment that their problems were predominantly emotional would have been an insinuation of malingering and probably have caused them to seek aid elsewhere. Typical of the patients in this group was a 39 year old woman who for two years had been plagued with pains originating in the intrascapular area. Consultations with an internist, orthopedist, and gynecologist, established the soundness of her health, but left her unsatisfied. A year later she was hospitalized for observation, at considerable expense, but learned again, somewhat to her dismay, that she was physically fit. Three months later she came to my office, was started on prochlorperazine, experienced moderate relief within three days, and continued to improve over a course of eight weeks' treatment. The response of others in this group more or less follows a similar pattern, and although these patients have been helped, none have progressed to the extent that they would accept an explanation that their physical illness, now relieved or nearly so, is a result of emotional conflict.

Prochlorperazine proved highly useful in aged patients who, because of restiveness and confusion, had become a domestic and often a social problem. It maintained them in a calm state without dulling mental processes. A dosage of 5 mg., t.i.d., proved successful in controlling all but one patient. The exception, a woman of 84 years, took the drug for three days, appeared to become more agitated, and immediately discontinued its use. In retrospect, a better response may have occurred had I, instead of treating the octogenarian, placed several of her high-strung, coddling daughters on the drug. With prochlorperazine, helping old folks who feel lonely, isolated, inadequate—even though surrounded by family—is a difficult task made less difficult.

Depressed patients benefited from prochlorperazine in that they, in contrast to their pre-treatment behavior, were able to sleep better, had more initiative about doing things, felt more sociable. Improvement was quite apparent in those whose depression stemmed from chronic stress and strain, not that prochlorperazine resolved emotional conflicts, but by providing a respite to those harried people, allowed them to reevaluate their situations and, with counselling, to cope with their problems or adjust to their handicaps. Menopausal patients, in particular, showed a satisfactory response, bene-

fiting as much from prochlorperazine as other menopausal patients did from estrogens.

Side effects, with prochlorperazine in dosages of 15-20 mg. were negligible. One patient developed stomatitis; one, drowsiness; and one, dizziness. Implicating prochlorperazine as causing stomatitis seems questionable. No evidence of blood dyscrasia, jaundice, or other serious untoward reactions, were encountered, even though many (68%) took the drug for three months and longer.

Comment

Evaluating drugs whose effects must be described in terms of behavior unfortunately lacks the precision attainable in studies where objective measurements are possible. The fundamental drawback is our inability to explain satisfactorily the etiology of mental illness on a physiologic basis. The findings of Heath[5] may ultimately lead to an explanation of the biochemical mechanisms of mental disease; he found that taraxein, a substance isolated from the serum of schizophrenics, produces episodes of schizophrenia when injected into normal humans. But, until these mechanisms are uncovered, evaluations of drugs such as prochlorperazine, even though elaborate behavior rating scales be used, will be a matter of impressions based on individual judgments, and be subject to the usual shortcomings.

The findings reported here, though subject to shortcomings, show the favorable results that can be obtained with prochlorperazine in controlling recurrent anxiety and its manifestations. They lead one to speculate about how prochlorperazine compares with established, similar-acting drugs, such as reserpine, chlorpromazine and meprobamate. Based on my experience with these drugs, prochlorperazine is equally effective in managing mild to moderately disturbed neurotic patients, such as those described here. Moreover, its remarkable freedom from drowsiness, depressing effects, and serious untoward reactions affords advantages in treating ambulatory patients. But, as with other tranquilizing agents, prochlorperazine is no substitute for psychotherapy, whether supportive or intensive. To use these drugs merely to provide symptomatic relief without attempting to help patients resolve or learn to live with their conflicts is hardly to be condoned.

Summary and Conclusion

Prochlorperazine was used to complement supportive therapy in 52 psychoneurotic patients and found effective for relieving symptoms of anxiety, tension, and apprehension. On a dose of 5 mg., three to four times daily, 17 obtained an excellent clinical response; 22, good; 5, fair; and 8 poor. A single dose of the drug in sustained release (Spansule capsules) form provided an effect that lasted approximately twelve hours. Patients on the drug regained the ability to relax, sleep better, and adjust more efficiently to disturbing environmental factors. Four of 5 patients on the verge of hospitalization responded adequately, becoming amenable to supportive psychotherapy on an ambulatory basis. Three patients reported side effects, one each of drowsiness, dizziness, and stomatitis. No jaundice, blood dyscrasias, or skin reactions occurred in the nine months the study required.

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346 Richey Ave., Collingswood, N. J.

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Dimethylane in the Treatment of Anxiety Reactions

JAMES M. A. WEISS, M.D., THOMAS T. FLYNN, M.D.,
and ROBERT M. COUNTS, M.D.
Assisted by K. WARNER SCHAIE, PH.D.

In recent years, a number of new pharmacologic agents have proved useful in providing symptomatic relief in various types of psychiatric disorders. This study reports an investigation and evaluation of the usefulness of one such relatively new drug, Dimethylane, in the control of anxiety and tension states.

In 1946 Berger and Bradley[1] reported that Myanesin and certain other simple monoethers of glycerol caused transient paralysis of voluntary skeletal muscles without respiratory embarrassment. It was also noted that these substances, in smaller doses, had a controlling influence on various types of tremors and other involuntary movements, as well as a relaxing effect on spasm, spasticity and rigidity. Gammon and Churchill[2] reported that Myanesin acted selectively on the basal ganglia, thalamus and brain stem; and Henneman, Kaplan and Unna[3] established the site of action of this drug as the internuncial cell, and further noted that Myanesin had a general sedative or tranquilizing effect. Berger, Bockelheide and Tarbell[4] found that characteristics similar to those described for Myanesin were also present in another series of compounds of quite different structure, the 2-substituted-4-hydroxymethyl-1, 3-dioxolanes, and that 2, 2-diisopropyl-4-hydroxymethyl-1, 3 - dioxolane —"Dimethylane"—possessed a wider margin of safety and greater activity than Myanesin.

Boines,[5,6] Boines and Horoschak,[7,8] and Kissen and Fortnum[9] investigated the use of Dimethylane in the treatment of "anxiety tension states" associated with primary dysmenorrhea (19 cases), menopause (40 cases), occupational stress (30 cases), and post-alcoholic reactions (25 cases). Improvement was noted in from 68 to 100 per cent of the cases in each study. Unfortunately, no control groups were used in any of these studies, and other drugs and/or procedures which might have affected the results were utilized in association with the experimental drug.

Vivino and Ritter[10] investigated the use of Dimethylane in the treatment of symptoms associated with primary dysmenorrhea (66 cases), and Kissen, Yaskin, Robertson, and Morgan[11] investigated the use of this drug in the treatment of post-alcoholic psychomotor agitation (42 cases). Again, improvement was noted in a majority of patients. In both of these latter studies control groups were used. However, the research designs appeared questionable in terms of selection of control subjects, knowledge by the experimenter of which patients received the drug and which did not, and, in the Kissen study, use of a potent drug rather than an inert placebo with the control group. It would appear, then, that in previous studies the effectiveness of Dimethylane in the treatment of various anxiety states and related conditions has not been clearly established.

Experimental Design

The present study was designed as a rigidly controlled "double blind" investigation. Subjects were selected according to clinically reproducible criteria designed to obtain a group as homogeneous as possible, so that the data obtained would be valid and reliable, inferences made would be quantitatively determined and methodologically sound, and the work would be suitable for replication. Criteria for patient selection were oriented primarily toward excluding from the study those persons who presented complicating factors that appeared likely to severely limit evaluation procedures, or to unnecessarily endanger the research structure of the study.

Starting in June 1954 all patients referred to the Malcolm Bliss Psychiatric Clinic at

From the Department of Psychiatry and Neurology, Washington University School of Medicine, and the Malcolm Bliss Psychiatric Hospital and Clinic, St. Louis, Missouri.

St. Louis City Hospital for consultation or out-patient treatment were evaluated as candidates for the program. The then current clinic policies excluded all non-residents of St. Louis, non-whites, or those under 17 years. Patients unable to speak or understand English were excluded, as were those who would have involved legal or administrative problems. All patients had previous medical examination, and those demonstrating signs of non-psychiatric physical illness which might contaminate results of the study were excluded. In addition, patients with psychiatric disorder of such severity as to require immediate hospitalization, patients with grossly questionable psychiatric diagnosis, and patients demonstrating definite signs of organic brain disorder or other psychotic disorder or mental deficiency, or personality disorder (in the diagnostic sense) were excluded. In general, patients selected were those diagnosed as suffering primarily from "anxiety reaction" as defined in the *Diagnostic and Statistical Manual: Mental Disorders.*[12] According to definition all patients included in this study manifested diffuse anxiety, "not controlled by any specific psychological defense mechanism as in other psychoneurotic reactions . . . characterized by anxious expectation and frequently associated with somatic symptomatology."

A further requirement was that all patients selected for the study should have primary symptoms which had been present (at least part of the time) for one or more months prior to admission to the study and were of frequency sufficient to be manifested several times per week. Patients who had acute symptoms with frequent periods of freedom from distress were not utilized.

The clinical procedure was relatively simple although strictly regulated. Each patient was interviewed and a record of his symptoms made. Present illness and relevant past history were noted and recorded in detail. Each person was then told by the examiner that he (the patient) would be given a medicine that should give him some relief from his symptoms. The patient was instructed not to take any other medicines (such as aspirin, codeine, or barbiturates) during this period and to return the following week. No other instructions were given and the patient was not told that he was participating in an experimental study. The patient was then introduced by the examiner to the clinic secretary and informed that henceforth he would receive his medication each week from the secretary.

Elaborate precautions were taken to make certain that neither the patient nor anyone in contact with him knew whether the patient was receiving drug or placebo. Drug and placebo were supplied in identical capsule form and in identical bottles except that Dimethylane bottles had white labels and placebo bottles had green labels. Until the end of the study, however, only one person (who was otherwise independent of the research team) knew which color label represented Dimethylane and which represented placebo. The bottles were kept by the clinic secretary, who put a week's supply of drug or placebo into plain prescription envelopes, on which was written only: "Take four capsules each day—one capsule after each meal and one capsule at bed time. Do not take any other medicines while you are taking these capsules." The clinic secretary knew, of course, whether patients were receiving "green label" or "white label" capsules, but she did not know which of these represented the drug. The two supplies of drug envelopes were kept in separate but adjoining areas, so that no patient knew he was receiving two types of medicines.

The basic design required that each patient be seen for an initial interview and then for four subsequent weekly interviews. Each patient received Dimethylane (or placebo) for two weeks, and then placebo (or Dimethylane) for two weeks. The dosage was four capsules daily, and each capsule of Dimethylane contained a 0.25 Gm. dose. Medication (drug or placebo) was started at the first visit and the patient continued to receive medication each week except at the final interview, which was used only for evaluation and disposition. Because other investigators using standardized dosages similar to ours noted improvement in comparatively short periods (ranging from several hours to one or two days, with a maximum lag before improvement of ten to fourteen days), it was our feeling that two two-week

periods, one on drug and one on placebo, should be sufficient. A random order selection for initial drug or initial placebo administration was used.

At follow-up interviews severity and frequency of symptoms, both as outlined subjectively by the patient and as evaluated objectively by the examiner, were determined. Any changes in severity or frequency of individual symptoms or the general level of tension or anxiety were noted. The patient's general judgment as to how he felt during that week was also noted. In addition, checks were made during each interview to determine if the patients had been taking the prescribed dosage of medicine. These follow-up interviews were limited to approximately fifteen minutes, and no attempt was made to employ intensive psychotherapy.

Levels of intensity for each specific symptom were recorded quantitatively on two five-point scales, one based on the patient's subjective judgment of improvement, and the other on the physician's objective judgment. Point values were assigned as follows: 0—worse, 1—no improvement, 2—slightly or questionably better, 3—definitely improved (some symptoms gone or all reduced), and 4—completely well and asymptomatic.

Results

A total of 315 patients were screened, and 30 of these met our criteria. Thirteen of the 30 were men, 17 were women. The age range was from 20 to 63 years, with a median age of 34. Twenty-two of the subjects were married, five were divorced or separated, two were widowed, and one was single. All were from lower or lower middle socio-economic classes.

As would be expected from the nature of our exclusion criteria, all patients used as subjects in the study complained of diffuse anxiety in terms of "anxious expectation," "general nervous tension," or "simple nervousness." In addition all except two patients complained of insomnia in some degree. Most patients had at least two or three additional complaints. About half complained of vague respiratory distress manifested by a "smothering sensation" or by occasional transient shortness of breath. About half of the patients mentioned either headaches (usually of the so-called "tension type") or vague generalized aches and pains, or both. Several patients complained of palpitation, anorexia, or vague "dizzy spells." A few patients complained of vague feelings of numbness, muscular tremors, "blackout" spells, vague abdominal distress, nausea, vomiting, constipation, diarrhea, urinary frequency, menstrual irregularities, dyspareunia or frigidity.

Ten patients otherwise not significantly different from the remaining 20 in terms of age, sex, or nature of symptoms, failed to return for the complete series of four follow-up interviews. Five patients failed after the first interview, four after two interviews, and one after three interviews. Although, of the total group of 30 subjects, half were started on Dimethylane and half on placebo, seven out of the nine patients who failed during the first two weeks were patients who had started on Dimethylane, and five of these failed to return after one prescription of the drug. Only three patients who were started on placebo failed to return for the complete series; two of these did so after two weeks on placebo and one after two weeks on placebo and one week on Dimethylane. These figures suggest that Dimethylane as compared with a placebo may have an effect which is somehow negative or unpleasant in initiating pharmacologic therapy.

Of the 20 subjects who completed the interview series, eight received Dimethylane during the first two weeks and placebo during the final two weeks of the treatment period, and twelve the reverse. As ratings of over-all change in the patients' general conditions were listed for each treatment week, there were available two sets of four ratings for each patient. One set of four ratings was determined by the patient himself, and one set by the examining physician. Two ratings in each set pertain to change observed after the patient had been taking Dimethylane, and two ratings to change observed after the patient had been taking placebo capsules. Table 1 shows mean ratings (using the five point scale noted above) for each of the four observations, for both

treatment groups: those who started on drug and those who started on placebo.

TABLE 1—*Mean Ratings of Over-all Change in General Condition of Patients Treated with Dimethylane and Placebo.*

Treatment Order	On Dimethylane		On Placebo	
	1st Week	2nd Week	1st Week	2nd Week
Self-rating by Patient:				
Dimethylane-Placebo	1.50	1.75	1.38	1.50
Placebo-Dimethylane	1.58	1.67	1.40	1.25
Rating by Examiner:				
Dimethylane-Placebo	1.50	1.50	1.50	1.50
Placebo-Dimethylane	1.50	1.75	1.50	1.58

NOTE: Rating point values were assigned as follows: 0—worse, 1—no improvement, 2—slightly or questionably better, 3—definitely improved (some symptoms gone or all reduced), and 4—completely well and asymptomatic.

It will be noted that patients generally demonstrated some improvement whether on drug or placebo, and there was a tendency for improvement with drug to be slightly greater than that with placebo. It should be remembered, however, that a rating of 1 indicates no improvement, and a rating of 2 indicates only slight or questionable improvement. The fact that patients improved (as measured both subjectively and objectively) with "treatment," whether given drug or placebo, was statistically significant, but the degree of improvement was very small. The apparent tendency for improvement with the drug to be slightly greater than that with placebo was also subjected to statistical analysis (analysis of variance). Whether the ratings were the patients' self ratings or those made by the observer, the individual differences within treatment groups were found to exceed the differences between conditions, so that the differences among mean scores noted in Table 1 are clearly attributable to chance.

The mean differences between drug and placebo treatment conditions were further analyzed separately for each week of the four week treatment course. No statistically significant differences were found except for the second week of the course, during which patients on Dimethylane did better (in terms of their own self-ratings) than those on placebo. Remembering, however that five out of the fifteen patients who had started on Dimethylane as compared with no patients out of the fifteen who had started on placebo had dropped out of the series at this point one would expect this specific difference might be statistically significant but not clinically significant.

A further statistical analysis was made of ratings of improvement for specific symptoms. Many different symptoms were reported by the patients, and analysis could be made only of the two most commonly reported complaints: "general nervousness" (or "general tension"), and insomnia. Tendencies toward improvement under the drug condition for general tension and under the placebo condition for insomnia, were noted. When the "t-test" for differences between correlated means was used to test the difference between mean ratings before and after two weeks of "treatment" on Dimethylane and two weeks of "treatment" on placebo, however, it was found that the observed changes were not statistically significant at the five per cent level of confidence.

Although adverse side effects such as vague gastric distress, nausea or vomiting, or drowsiness had been noted in about four per cent of the 222 cases previously investigated by other authors, in our series there were no adverse side effects which could be clearly attributed to Dimethylane.

Comment

The present study appears to further substantiate the validity of suggestions made by numerous authorities that, particularly in the field of psychiatric therapy, rigidly controlled research studies are prerequisite to making sound inferences as to the value of any particular kind of treatment. Special care must be taken to avoid any kind of conscious, preconscious, or unconscious influence of the results on the part of experimenter or his co-workers.

It is of interest although not a novel finding, that our patients generally demonstrated slight (and probably transitory) improvement whether they received drug or placebo. Two of us later attempted to treat several similar patients by utilizing similar schedules of brief directive contacts without giving the patients any "medicine" (placebo or

drug) whatsoever. With such treatment the slight improvement noted in patients afforded brief psychiatric contacts and "medicine" was not apparent.

After analysis of the data collected in this study, then, it was our final impression that Dimethylane is of little value in providing symptomatic relief for patients suffering from generalized anxiety reactions. The reader might ask whether different results might have been obtained had we used a larger number of subjects. It is possible that with 100, 1000, or 10,000 subjects we might have found Dimethylane to be more effective than was indicated in the present study. From the statistical point of view, however, extrapolation of our data makes it highly probable that if any statistically significant differences were to be noted between effectiveness of drug and placebo in a larger series, such differences would be very small and of little clinical significance. It would seem to be wasteful of time and effort to attempt more extensive investigation.

Another question might be raised: How could we be sure that the patients actually ingested the drug (or placebo) capsules? Subjects were questioned on this point at each follow-up interview, and the interviewers relied on their experience as psychiatrists to determine whether or not the information given by the patients was reliable. We also felt that the study was so planned that deviations from the established routine by the subjects would be effectively scattered between placebo and drug groups, and would therefore not significantly influence the results.

Our results do not rule out the possibility that Dimethylane might be of value in the control of symptoms other than generalized anxiety, particularly symptoms more directly associated with muscular spasm, spasticity or rigidity. In terms of earlier studies, further investigation of the use of Dimethylane in the treatment of symptoms associated with primary dysmenorrhea and post-alcoholic psychomotor agitation seems warranted.

Summary

This study reports an investigation and evaluation of the usefulness of a comparatively new drug, Dimethylane (2, 2-diisopropyl-4-hydroxymethyl-1, 3-dioxolane), in the control of anxiety and tension states. A rigidly controlled "double blind" method of investigation was used. Thirty patients with a primary diagnosis of "anxiety reaction" were carefully selected according to defined criteria. Half of the patients were given drug capsules for two weeks and then placebo capsules for two weeks, and for the other half the order was reversed. The capsules were identical and elaborate precautions were taken to make certain that neither the patient nor anyone in contact with him knew whether the patient was receiving drug or placebo. Evaluations on quantifiable scales of any change in frequency or severity of symptoms were made by both patients and examiners.

Patients generally demonstrated slight improvement, whether given Dimethylane or placebo. Contrary to the conclusions of some previous studies, most of which did not use control groups, no significant differences were found in the effects of the drug as compared to those of the placebo. In our series there were no adverse side effects which could be clearly attributed to the drug.

It was our final impression that Dimethylane is of little clinical value in providing symptomatic relief for patients suffering from generalized anxiety reactions, but that further investigation of this drug in the control of symptoms associated with such specific conditions as primary dysmenorrhea and post-alcoholic psychomotor agitation seems warranted.

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Electroshock Therapy Without Muscle Relaxants

J. M. RADZINSKI, M.D.

The purpose of this article is twofold: 1) to evaluate critically some of the methods now being used in combating complications of electroshock therapy and 2) to show that shock therapy without muscle relaxants is reasonably safe not only in healthy individuals but in a great variety of poor physical risks. The latter point especially requires clarification on medico-legal grounds because of intimations by some users of relaxant drugs that non-employment of these latest "advances" in electroshock technique borders on negligence on the part of the therapist.

After two decades of convulsive therapies, the problem of complications, notably fractures and occasionally death, continues to haunt the therapist. Although many statistics on the incidence of fractures in the course of electric treatments have been published, there is little agreement among them. Nor have the dynamics of spinal fractures been elucidated to the satisfaction of all concerned. The following table illustrates the wide discrepancy in the reported incidence of fractures:

TABLE I

Authors	No. Patients	% Fractures
Kolb & Vogel[14]	1000	.9%
Samuel[14]	420	2.8%
J. P. Kelly[14]	2200	2.3%
Langley & Robbins[15]	230	23.0%
Meshan, Calhoun & Scruggs	212 M	35.4%
Dewald, Mergolis, Weiner	263	20.8%
Huddleson & Gordon	252	6.3%

Aside from the question of error of observation, the incidence of fractures appears to depend on three factors: 1) the condition of the skeleto-muscular system of the patient, 2) type of restraint, 3) severity of convulsion. The last, in turn, is dependent on the type of current used. Since in general psychiatric practice patients of all physical types and states come for treatment, there remain but two factors to consider, restraint and the type of current. Restraint may be effected either by mechanical or chemical methods.

On the question of mechanical restraint, the trial and error method has followed the full gamut from rigid restraint of all major vulnerable skeletal points to complete avoidance of restraint. Paul Cossa[1] attributes the fewer reported fractures in France to less emphasis on restraint. Since the majority of skeletal complications occur in the dorsal spine, the general practice has been to favor extension of the spine by means of pillows or a Gatch bed. Kalinowsky[2] has abandoned this practice and now treats his patients in slight flexion.

Search for a current most suitable in shock therapy has stimulated experimentation with various currents with the object of softening the seizure or limiting it to a part of the body. To be sure, fractures have been reduced, if not eliminated by such currents, but at the cost of the subjective comfort of the patient. The gentler the effec-

tive current the greater the likelihood of its being felt and subsequently dreaded by the patient. I recall during my experimentation with "softer" currents how one young female patient never did forgive me for inflicting upon her temples the sensation of "a blow with a baseball bat."

The intolerable subjective discomfort associated with soft electrical procedures has led to the introduction of narcotizing and paralyzing drugs. The first preparation used extensively in the forties was D tubo-curarine. Because of the sensation of suffocation associated with the paralytic stage, it was found necessary to narcotize the patient with pentothal. Although soon after the introduction of curare alarming reports of deaths and near deaths began to appear in the literature, A. E. Bennett,[3] a pioneer in the field, as late as 1948 expressed strong approval of the curare technique.

It became clear, however, that the safety margin of curare was too narrow for comfort particularly in view of the fact that some individuals show a hypersensitivity to the drug. Even with adequate oxygen intake, some patients died, either because of an unfavorable central action of curare or from a complicating bronchospasm and circulatory collapse from a histamine-like effect.

Quest for safer relaxants brought on the market such synthetic preparations as flaxedyl and syncurine. These also were found to be dangerous. W. S. Maclay,[4] in an excellent survey of treatment fatalities in England, collected 62 cases of death in the course of ECT. Of these cases, 28 had been premedicated with relaxant and other drugs. A number of these patients had previously tolerated straight ECT. Four of the patients died from the medication before the electric button was pressed.

Today, succinylcholine chloride (Anectine) is being recommended as answering all reasonable requirements of safety. An analysis of a typical report on the use of this drug leaves this writer unconvinced. W. P. Wilson and W. K. Nowill[5] employed Anectine in 168 patients with a total of 1045 treatments. Apnea occurred in 100 of the patients, its average duration being 1.9 minutes. Two patients had an apea of 10 minutes each. There was one fracture in this series involving the right transverse process of the fourth cervical vertebra. Another patient developed a mild aspiration pneumonia. A third aspirated a small amount of vomitus and subsequently developed atalectasis of the right lung. "Prompt bronchial aspiration, inflation of the atalectatic lung and antibiotic therapy resulted in complete disappearance of the symptoms and X-ray findings in 24 hours."

Both curare and its synthetic equivalents affect the vital respiratory function. The efficacy of these drugs depends on premedication with atropin and an intravenous barbiturate—another respiratory depressant. Oxygen must be available for controlled respiration. Air passages must be kept clear of mucus etc. Thus an operational chain, no stronger than its weakest link, is forged to guard against the iatrogenic complications of respiratory arrest, atalectasis, aspiration pneumonia and circulatory collapse.

One cannot but note with misgivings the growing tendency among some therapists towards hazardous polypharmacy. At times it seems that the eager psychiatrist seeks to tempt fortune by skirting at the brink of disaster. Let me cite an example: A greatly disturbed male patient, 28 yrs. old, received on the day preceding his last ECT 800 mgms of Thorazine, 200 of it IM. Next morning he is given an inhalation of nitrous oxide (30 sec.), followed by inhalation of CO_2 in 70% oxygen (duration unspecified). This was followed by the ECT and then by "subconvulsive diencephalic stimulation," in the course of which he died.

While some therapists exceed the limits of ordinary prudence by overmedication with potent pharmacologic agents, a few seem to have an attraction for the shock machine itself with the result that the patient is exposed to what may be called an iatrogenic status epilepticus. An example: "After intravenous injection of 2 cc of curare, the machine was set at 70 volts for .4 sec. and a stimulus administered. Immediately after the initial convulsion, the stimulus was repeated. This was done four times." The patient, a 54 yr. old male, died after the fifth procedure.

The first principle in medical practice has

always been to avoid harm—*nil nocere*. Interference with the vital functions of respiration and circulation is justified only as a life saving measure. Outside of certain psychiatric emergencies, such as extreme excitement leading to exhaustion or an irrepressible suicidal urge, the role of shock therapy is mainly to shorten the course of a psychosis or to render a disturbed patient more tractable. It still remains to be proved whether in the schizophrenic group more patients recover with ECT than would eventually get well by other methods. Moreover, the relatively benign nature of electroshock complications renders dubious any need of placing the vital functions in jeopardy.

The theory that the pentothal-Anectine technique is easier on cardiac and otherwise debilitated patients is likewise open to question. Debilitated individuals in consequence of their wasted musculature have milder seizures than others. As for the lightened strain on the circulation with Anectine, there are indications that the opposite may actually be true. Studies by William L. Holt and associates[7] with Flaxedil and Anectine show a marked fluctuation in blood pressure from an initial drop to a secondary rise with Flaxedil and a somewhat smaller fluctuation with Anectine. But more arrhythmias were found with the latter. One patient on Flaxedil registered a drop in systolic pressure from 180 mm Hg. to 70 mm.—a near catastrophic effect.

Many workers have rightly expressed the opinion that muscle relaxants have substituted equal, if not greater, hazards in the respiratory and circulatory systems for those they are supposed to solve in the skeletal system.[2,8,9,10] A recent letter by Kalinowsky[11] reported correspondence with two European workers, one of whom had one and the other two fatalities with Anectine. Some workers, following Impastato's method, now avoid the hazards of Pentothal in their use of Anectine by first rendering the patient unconscious with a petit mal stimulus before administering the convulsive dose of current.

Relaxant drugs have not been alone in increasing hazards for the patient. Deaths have been reported with combined electroshock Thorazine and electroshock Serpasil therapy.[12] At the recent panel discussion on electroshock at the APA meeting in Chicago (1956) the discussants who had used such combinations reported that when the patient dies "he goes out like a light."

The exact dynamics of spinal compressions which have been responsible for much of the relaxant controversy remain uncertain. One theory is that the fracture occurs as a result of a sudden flexion of the upper spine during the initial phase of the convulsion.[18] Another theory is that the upper thoracic spine, the neck and the skull are compressed downwards by the longitudinal spinal musculature delivering a "hammer type" blow to the joint surfaces of the vertebral bodies.[13] The "wedging" of the compressed vertebral bodies is explained by the simultaneous operation of both processes. It is doubtful whether the contraction of the relatively weak upper spinal musculature alone would be sufficient to crush a vertebra. It is more likely that the massive lumbosacral flexors and the abdominal muscles by tending to approximate the pubis to the xiphoid process indirectly contribute the decisive force in the crushing action. Why fractures occur in the upper dorsal spine has been explained by the more delicate structure of the vertebral bodies in that area and by their relative immobility. It has been shown that of all the dorsal vertebrae, the fifth is the least movable and the most readily crushed experimentally.[2] It, therefore, may be regarded as the center of dorsal vulnerability and as the fulcrum from which the two ends of the spine extend cephalad and caudad as levers. Powerful flexor action at both extremities of the spine thus tend to converge towards the region of the fifth dorsal vertebra as the apex with crushing effect.

If these dynamics of spinal compressions are correct then prevention would be promoted by a more effective immobilization at both ends of the spine during treatment. I shall later describe a practical application of this theory.

During the past 18 years I have treated at St. Mary of Nazareth Hospital and at Pinel Sanitarium in Chicago about 2,000 psychiatric patients with a total of approximately 14,000 treatments without the use of relaxant drugs. The patients were of both sexes, though females predominated, and

ranged in age from 16 to 85 yrs. There has been no fatality.

One gets the impression while observing these patients after treatment and watching the healthy glow of their flushed faces that they benefit not only from the central action of the current but from the stimulating metabolic effect of the convulsion itself. The muscle soreness of which many previously inactive patients complain following treatment is the same healthy soreness that normal persons find not unpleasant after vigorous exercise.

During the past two years, 233 patients received a total of 1643 treatments. Among them there were 29 with organic cardiovascular disease. Their clinical diagnoses confirmed by EKG were as follows:

Hypertensive heart disease	6
Coronary insufficiency	10
Intraventricular block	3
Frequent auricular and ventricular extrasystoles	3
Old infarctions	3
Mitral stenosis	2
Auricular fibrillation	2

Only those cases were included in the hypertensive group whose systolic pressure was persistently 200 mm. Hg. or more. One 59 yr. old depressed male had a pressure of 260/150. He received 12 ECT with recovery. Another patient, a 27 yr. old female, had advanced chronic rheumatic valvular disease bordering on decompensation and with auricular fibrillation. Cardiac patients were given atropin and a short period of oxygen inhalation before and after treatment.

Two women in their ninth month of pregnancy received six treatments each without complications.

The record of skeletal complications was studied systematically from July 1955 through August 1956. During this time 125 patients received 884 treatments. It was possible to obtain pre- and post-treatment X-rays in 87 of these cases. Among them were 23 repeaters with a history of one or more courses of ECT. There were 64 new cases. The results of this study are summarized in Table 2.

TABLE 2

	Total	Male	Female	Fracture	No. Comp. Vertebrae
Old Cases	23	6	17	7 F 2 M 3 M	24
New Cases	64	14	50	3 F	10

The incidence of fractures discovered in the repeaters was 39%, in the new patients 9.5%. The difference in these figures is more striking when we consider that in the old cases there were 2.6 compressed vertebrae per fracture patient, in the new the ratio was 1.7. Three of the six new cases had only a mild degree of compression consisting of cupping of the dorsal surfaces with a slight decrease in the height of the vertebral bodies. The compression in the remaining three was moderate according to the classification described by Newbury and Etter.[14] The number of old cases is too small to have a significant statistical value though these patients were selected only on the basis of recurrence of the psychosis. Perhaps the high rate of compressions found among them is due to the fact that they had been treated with a machine giving an instantaneous rise of current. In the present series an apparatus with a glissando current was used. None of the patients with old compressions suffered any backache or any changes in the X-ray findings following their most recent ECT.

Among the 64 new patients there were five, aged 62 to 67 with advanced osteoarthritic changes in the spine, one with a marked rotary scoliosis and one 54 yr. old female with osteoporosis. None of these developed compressions or backache after treatment.

In this series of cases an attempt was made to neutralize the flexion factor in spinal compressions not by manual restraint of the lower extremities but by the use of a specially constructed belt applied to the pelvic region. The belt, shown in Fig. 1, is made of strong canvas 10 inches wide and long enough to pass across the bed or treatment table. The segment of the belt overlying the patient's pelvis is padded with a layer of foam rubber 3-4 cm. thick. Three leather straps passing under the bed frame are used to secure the belt in position. The foam rubber permits an elastic restraint to

the contour of the pelvis without being rigidly unyielding. The belt is fastened with decreasing tightness from above downwards to allow some flexion of the thighs without danger of bruising the thigh muscles. At the cephalic end of the spine, the head is held firmly and under traction to counteract the "hammer type" effect of the contraction of the longitudinal spinal muscles. (Fig. 1.)

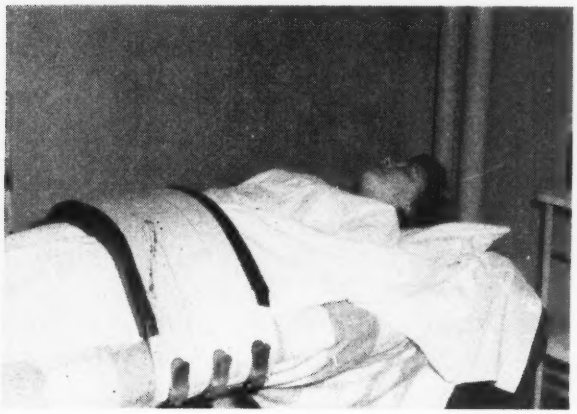

Fig. 1.

The foam rubber belt has been found useful not only in limiting pelvic flexion during the seizure but as an effective restraint during the post-seizural excitement. It is less in the field of returning consciousness than wrist and ankle restraints. In patients with herniae or recent abdominal scars, it serves as an adequate abdominal support. Based on the series listed above, the belt appears to reduce the frequency and severity of compressions.

Summary and Conclusion

The subject of electroshock therapy has been reviewed from the point of view of the commoner skeletal complications and the various methods designed to prevent them. The subject of relaxant drugs has been discussed and their hazards pointed out. Survey of the literature shows that while electroshock therapy without relaxant drugs carries a higher rate of skeletal injuries, the great majority of these are not disabling. On the other hand, use of relaxant drugs unquestionably increases the risk of a fatal accident. In weighing the relative merits of shock therapy with or without relaxants, the therapist might well ask himself the question: How many vertebral compressions would he be willing to trade for one fatality traceable to a relaxant drug? On the subject of risks associated with cardio-vascular disease, it appears that if a patient can tolerate ECT combined with a barbiturate-relaxant cocktail, he can take it straight as well. A certain irreducible minimum of cardiac deaths will occur under any circumstances because the existing clinical and laboratory methods cannot predict accurately an impending coronary accident.

The use of a foam rubber belt is described which appears to aid in decreasing the incidence and severity of spinal compressions.

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Preliminary Report on Cytopathology of Erythrocytes of Schizophrenic Patients

H. R. ANSLEY, W. H. SHELDON, M.D., A. M. TENNEY and R. D. ELDERKIN

Introduction

In the course of a blood study of schizophrenia a case of anisocytosis was observed in which erythrocyte diameters ranged from 1.2 to 9.2 microns. Although such a condition was observed, or at least was obvious, only in the one case, measurements were made of erythrocyte diameters of all the patients under study and a control group of normal individuals was run for comparison. The results suggest that cases of anisocytosis in schizophrenia may not be exceptional but more or less present as a concomitant of the disorder.

Methods and Results

Camera lucida drawings were made of wet films and Wright-stained preparations of peripheral blood. Samples of a hundred cells from each individual were found to give reproducible mean diameters. Abnormals and controls were alike as to age, sex and race. In addition to the usual precautions both groups were somatotyped in order to control differences in body build, said to be a factor in size of erythrocytes.[1] Each group showed approximately a normal distribution for somatotype.[2] Secondary components of somatotype were also gauged and the distribution of the two groups was found to be alike with respect to the so-called "textural" variables, which had been suspected of histological origin.[3] So far as was possible the major difference between the groups was limited to the factor of chronic schizophrenia. This was not only a major difference but a complex one as well. Hospital diagnoses included simple, hebephrenic, paranoid, catatonic and mixed.

For ease of comparison the data are arranged in descending order of magnitude. Means and standard deviations of the mean are presented in separate columns, as there

MEAN DIAMETERS OF ERYTHROCYTES IN MICRONS (Wright-stained preparations)		STANDARD DEVIATIONS OF THE MEAN (Wright-stained preparations)	
Patients	Controls	Patients	Controls
8.32	8.10	2.20	.74
8.30	8.10	1.70	.70
8.26	8.06	1.52	.63
8.25	7.98	1.39	.60
8.13	7.96	1.37	.57
8.10	7.79	1.36	.56
8.02	7.78	1.34	.55
7.91	7.75	1.34	.55
7.83	7.70	1.26	.55
7.76	7.67	.88	.54
7.72	7.67	.86	.54
7.70	7.59	.84	.53
7.65	7.58	.79	.52
7.55	7.55	.68	.50
7.53	7.54	.61	.50
7.43	7.47	.60	.48
7.41	7.35	.60	.44
7.38	7.10	.57	.32
7.25		.56	
7.22	av. m=7.71	.52	av.=.546
5.98		.50	
m=7.70		av.=1.023	

Biology Department, Johns Hopkins University, Baltimore, Md.; Constitution Clinic, College of Physicians and Surgeons, Columbia University, New York, N. Y.; Research Facility of Rockland State Hospital, Orangeburg, N. Y.

This study was supported by the Biological Humanics Foundation and the Research Facility, Rockland State Hospital.

is no correlation between variance and mean. The standard deviations do not, therefore, correspond with the mean values opposite them.

Although the abnormal group shows a greater range of mean diameters, the group means are the same. No great significance is placed on cell diameter per se in this study. The standard deviations are what distinguish the two groups, the larger standard deviations of the abnormals reflecting anisocytosis. The group standard deviation of the abnormals is about twice that of the normal group with very little overlap between the ordered ranks. Statistical comparison is difficult because of skewed distribution in the abnormal group. The nonparametric Mann-Whitney U-test applies to such a case, since no assumption concerning distribution or sample-structure is made.[4] This test yields the equivalent of a t-value of 3.9 for Wright-stained preparations and of 5.2 for wet films. The probability that the anisocytosis of the schizophrenic group as a whole is normal is therefore negligible by any standard, whether the cells are fixed and dried or living.

Discussion

The small size of the sample makes the results only suggestive, but one point of interest is raised. A high variance is found in a morphological character rather than a physiological one. Thus the homeostatic imbalance after associated with schizophrenia may be even more profound than usually postulated. The anisocytosis may be a consequence of physiological disturbances. On the other hand the physiological disturbances may result from a primary imbalance of the cells. Homeostatic imbalance is associated with the expression of recessive genes; inbred lines are physiologically more variable than F_1 hybrid populations, although both are genetically homogeneous.[5] If schizophrenia has a genetic etiology, then the anisocytosis suggested by these findings may indicate an organism which is poorly buffered against environmental stress even in hemopoiesis.

Summary

Variance of erythrocyte diameters is found to characterize a group of schizophrenic patients when compared with normals. Thus the homeostatic imbalance of schizophrenia is extended to include a character of blood morphology in addition to the well-known disturbances of blood chemistry.

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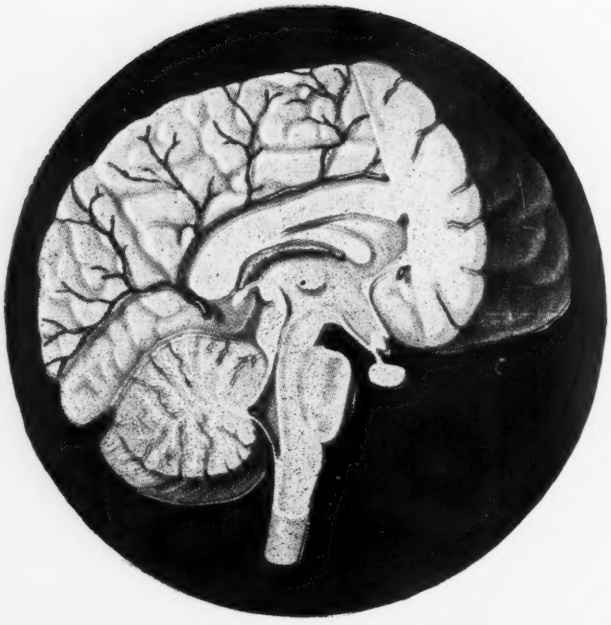

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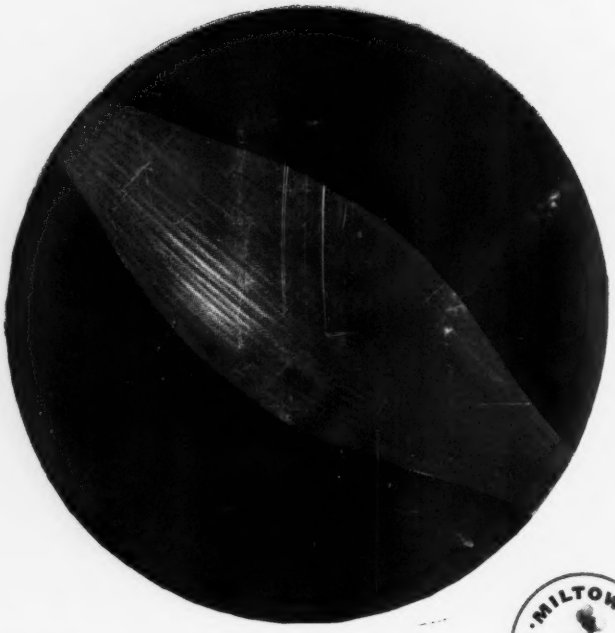

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